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THE OPERATIVE TREATMENT OF CARCINOMA OF THE CERVIX RADICAL PANHYSTERECTOMY WITH PELVIC LYMPH NODE EXCISION

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THE general revival of interest in the surgical treatment of cancer of the cervix is a natural sequence to the extension of the surgical attack upon malignant neoplastic disease in general which is one of the characteristic features of surgery in the past decade and a half. It would appear, therefore, that a brief reconsideration of the historical background of the operative treatment of cervical cancer is not out of order in connection with a presentation of a radical form of panhysterectomy and pelvic lymph node excision carried out by the author in the past three years at the Memorial Hospital.

The earliest attempts to eradicate cervical cancer consisted of operations limited to the cervix and were foredoomed to failure. In the pre-Listerian epoch, according to Leonardo, Walter Burnham, of Lowell, Mass., performed the first total hysterectomy for malignant disease of the uterus under the clinical diagnosis of ovarian cyst but the true condition was found to be "sarcomatous disease" of the uterus (1853). Freund's first reported total hysterectomy, in 1878, is commonly regarded as the beginning of the modern era in this field. It is to be noted that, as early as 1895, comparison was made between the surgical problem of carcinoma of the cervix and pelvic lymph nodes and the surgical problem of carcinoma of the breast and axillary nodes. (Emil Ries discussed this question in suggesting that the pelvic lymph nodes be systematically excised together with the performance of a total hysterectomy.) In 1896, J. G. Clark, then Resident Surgeon in the Gynecological Department at the Johns Hopkins Hospital, reported upon 10 patients in whom panhysterectomy with excision of parametria had been performed and in addition the group of lymph nodes about the bifurcation of the common iliac vessels were enucleated digitally. This report was published prior to Wertheim's original article but so great was the influence of Viennese gynecology that Wertheim's name was soon applied to

the operation. In 1898, Werder described the mobilization of the uterus and adnexa from above, peritonization over them, closure of the abdomen, and then removal of these structures from below per vaginam. T. S. Cullen's monograph on cancer of the uterus, which dealt with the pathology and surgical treatment, appeared in 1900, and is the first comprehensive work on the subject in the American literature. Sixty-one patients are cited in whom operation was performed "but the results are most distressing."

It was realized from the beginning that a more or less localized operation did not yield the desired results and it was appreciated that an important factor in this situation was failure to excise the pelvic lymph nodes and areolar tissues. Yet some were of the opinion that if once metastases invaded the pelvic nodes, the patients were lost and so there was little to be concerned about when the situation was hopeless. Wertheim in 1912 wrote: "In reference to the regional lymph glands we hold the same views as formerly, that we remove them only when they are found to be enlarged. This question has been attacked from various points. Against the demand that the principal thing is to remove all of the lymphatic system is the fact that first of all this could not be accomplished and second it is not necessary to do so. Admitted even that in some few cases carcinoma metastases may be found in glands slightly enlarged say to the size of a pea, yet it is a fact that in spindle-shaped glands normally found in the pelvis and becoming swollen with chain-like formation no carcinoma is ever found." It is of interest to compare this statement with that written by Weibel, Wertheim's first assistant, one year later: "These two points characterize the radical operation [Wertheim's]: widest excision of the parametria and removal of the pelvic glands." In 1913, J. G. Clark, now in Philadelphia, wrote: "With increasing experience the difficulty and even the impossibility of really executing a truly extensive glandular dissection caused me to abandon this attempt: for it unduly lengthened the time of operation with a considerable increase in primary mortality as well as an increase in operative mishaps and post-operative complications. Hence I confine my efforts to the widest possible excision of the parametria with as large a vaginal cuff as possible, contenting myself with the removal of one or more glands if palpably enlarged for prognostic purposes." In the same year, Neel, summarizing the work in Howard T. Kelly's clinic, stated: "As it is generally conceded that the lymphatic glands are implicated in from one-third to one-half of all operable cases, and since we have no means of determining that involvement except by microscopic examination, theoretically speaking the ideal operation would include their resection in all cases. However, the present operative facilities and technique do not justify such an extensive operation on account of the great increase in the primary mortality following such a procedure. Hence for many years no attempt at removal of the lymph structures other than those of the parametria has been made."

Latzko (1895) also advocated a systematic removal of pelvic nodes and areolar tissues in conjunction with radical panhysterectomy of the so-called Wertheim type. His ideas are cited in a number of articles, especially in the first two decades of this century, and his operation is illustrated in texts on gynecologic surgery (Peham and Amreich; Halban), yet it is not possible to find reported a significant series of patients subjected to the procedure. According to Ludwig Adler, Latzko's operation was not frequently carried out and finally was given up because of the high morbidity and mortality which accompanied it at the time.

The question of the radical vaginal excision of the uterus for cervical cancer (Schauta operation) will not be considered here because a wide excision of pelvic lymph nodes cannot be performed by this approach.

With the advent of irradiation therapy interest in the surgical attack was greatly curtailed. However, it was generally appreciated that pelvic lymph

node metastases could not be easily, if at all, controlled by irradiation and for this reason Taussig raised the question of surgical excision of lymph nodes, leaving the irradiated uterus in situ. The impression is gained by reading Taussig's last article published in 1943 (his Fig. 6), that emphasis was placed upon removal of individual or groups of nodes rather than en masse removal of areolar tissue in continuity as well as nodes. More recent reports by Morton and by Nathanson would indicate that there is little to be expected from such procedures.

Bonney, in England, persisted in a surgical program for the treatment of carcinoma of the cervix emphasizing the excision of obturator nodes and external iliac nodes after the panhysterectomy. In this country Lynch and Masson were among those who never did abandon the surgical treatment and in recent years J. V. Meigs has very poignantly raised the issue again of the surgical treatment, showing that in selected patients with small lesions, the surgical mortality could be maintained at least as low as that imputed to irradiation.

If it is now feasible to carry out systematically an extensive pelvic lymph node excision, the reason is not greater dexterity on the part of surgeons today as compared with those of a previous era but it is due to the most effective pre- and postoperative supportive therapy that has evolved in recent years, especially in regard to anesthesiology and the prophylaxis and treatment of surgical shock.

Preoperative Preparation

Blood studies are made to insure that the erythrocyte count, hemoglobin, and hematocrit are within normal limits. Blood chemistry determinations are made for blood urea nitrogen, chlorides, glucose, and plasma proteins. Abnormalities are corrected. If there has been appreciable loss in weight, blood volume determinations are made and blood given to secure maximal optimum circulating blood volume. In depleted patients, vitamin C is given in doses of 1,000 mg. daily; also vitamins B and K are administered in adequate quantities.

Preoperative intravenous pyelograms are made to check on the status of the urinary tract, also for comparison with similar roentgenograms that may be necessary later. When there is a question of bladder involvement, a cystoscopic examination should be performed.

The bowel is emptied by purgation with castor oil the third and second nights before operation and magnesium sulfate solution the second and first mornings before operation. The advantages of an empty bowel are obvious; retraction of the intestines out of the pelvis is facilitated and entrance into the bowel by accident is rendered less hazardous. Furthermore, if ureteral transplantation into the colon becomes necessary, preparation of the colon has been made.

Regular diet is permitted to the evening before operation and the day before operation 1,500 c.c. of 5 per cent dextrose in saline are given intravenously to compensate for fluid loss by catharsis.

In the operating room facilities for adequate blood transfusion are available, including measures for ultra-rapid transfusion should this be necessary (Pierce and associates). Type specific blood is employed. Prior to incision the intravenous infusion is in function with the use of a No. 13 needle with saline solution in the flask. Blood infusion is started as the operation begins.

Operative Procedure

1. The patient is placed in the Trendelenburg position. A low midline incision is made, which curves to right or left of the umbilicus and extends upward for 4 to 6 cm. above the umbilicus.

2. After retraction upward of the small intestines (or if more room is necessary the small bowels are permitted to lie outside of the abdomen, falling caudad and covered with moist towels) the right ovarian ligament is secured between hemostats and divided. This permits entrance into the right lateral extraperitoneal pelvic space. The finger is inserted downward and outward to enlarge the rent in the peritoneum. The latter is then enlarged upward. At this point the position of the ureter is located and kept in mind. The upper limit of the opening in the peritoneum should expose the right side of the bifurcation of the aorta and vena cava. Distally the opening is enlarged by transection of the round ligament.

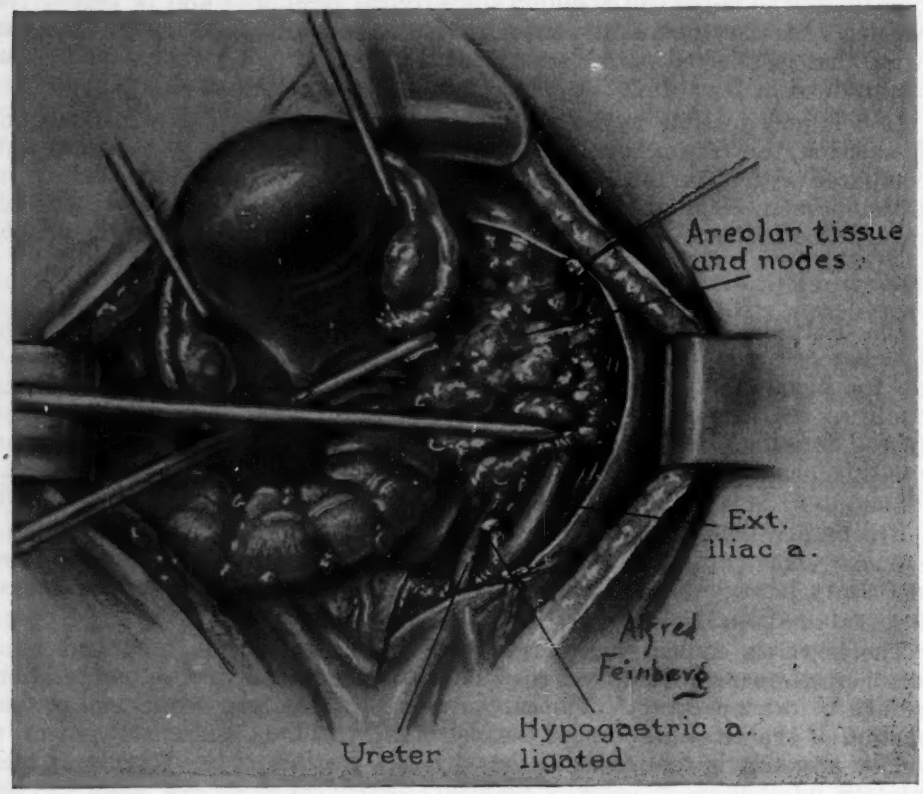


Fig. 1.—Right ovarian ligament has been divided, nodes and areolar tissues over right common iliac vessels have been removed or swept downward and mesially, and similar dissection is begun over external iliac vessels. The hypogastric artery is shown divided but this step may be carried out at a later stage after the right pelvic nodes and areolar tissues have been dissected free.

3. With a dissector and thumb forceps the areolar tissues and lymph nodes over the first portion of the common iliac vessels are dissected from the walls of these vessels and the dissection carried downward (Fig. 1). Vigorous bleeding will usually be encountered from small vessels coming from the common iliacs to the nodes and areolar tissues. These are severed and ligated. The lymph nodes and areolar tissues are swept downward and off the external iliac artery.

4. By means of a dissector an opening is made into the areolar tissues mesial to and below the external iliac vein which lies below the artery (Fig. 2). The index finger inserted into this opening is directed laterally until the finger-

tip touches the lateral pelvic wall and is then swept anteriorly and posteriorly, gently peeling away areolar tissues and lymph nodes from light attachment to the pelvic wall and lateral pelvic floor. In this manner the contents of the obturator fossa are also mobilized and pressed medially. The obturator nerve is sought for in the tissue and by digital dissection freed from the areolar tissue and permitted to fall laterally toward the pelvic wall where it then remains denuded. The index finger is then hooked under the peritoneal reflection from the anterior lateral pelvic wall onto the anterior lateral bladder surface and this bridge of peritoneum incised.

5. Attention is now directed to the hypogastric artery which is isolated, divided, and ligated. Great care must be exercised in avoiding injury to the underlying large thin-walled hypogastric veins. The latter are sometimes isolated and divided. There is considerable variation in their numbers and pattern of distribution.

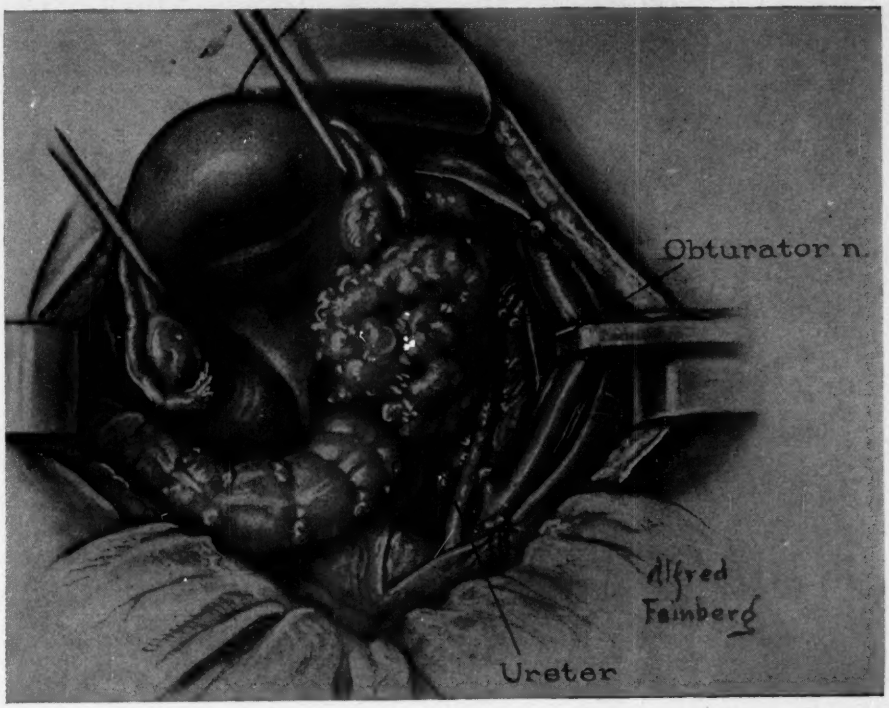


Fig. 2.—Lymph nodes and areolar tissues over external iliac vessels and in obturator fossa have been freed and retracted mesially to exposure and denudation of musculofascial pelvic floor. The obturator nerve is completely exposed and remains uninjured but if it is accidentally divided no appreciable disturbances will result.

6. As the areolar tissue is packed gently mesialward, veins and arterial branches are exposed, ligated, and divided. Lymph nodes and areolar tissues over the hypogastric vessels encountered are excised or swept downward and mesially against the detached broad ligament areolar tissues. This mobilization of tissue is carried downward to the musculofascial pelvic floor which is denuded and the areolar tissues over the three great nerve trunks forming the sciatic nerve are also stripped away denuding these nerves.

7. The ureter is observed and areolar tissues over its lateral aspects swept downward. The tip of the index finger is inserted into the ureteral "tunnel" in the broad ligament to enlarge it and the upper outer portions incised to expose the ureter to the bladder. In this step large uterine veins and the uterine

artery will be opened and must be secured and ligated. The ureter is never stripped of areolar tissue but a modicum of this tissue is left about it in order to avoid sloughing with fistula formation. This point in the procedure is perhaps the weakest phase since near the cancerous cervix the periureteral areolar tissue is likely to be invaded by disease and yet must be left in situ.

8. The peritoneal reflection from bladder to uterus is incised transversely and the bladder is peeled forward, care being exercised to avoid injury to the ureters (Fig. 3).

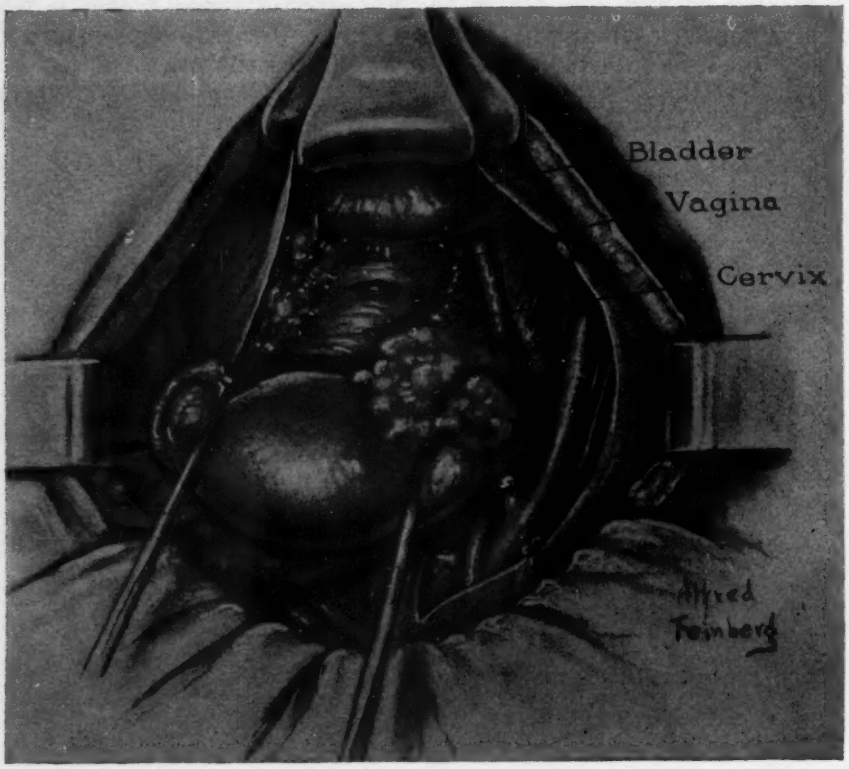


Fig. 3.—Radical dissection of the right side of the pelvis has been completed. The ureter has been freed to the bladder and separation of the bladder from the anterior vaginal wall has been started.

9. At this point the dissection is then carried to the left side. The peritoneum is incised in a manner to permit upward retraction of the sigmoid. The left ovarian ligament is divided between clamps and the areolar tissues and nodes over the left common iliac vessels are dissected downward. There are usually fewer nodes along the left common iliacs than on the right side; frequently there are no nodes on the left common iliac vessels. The left hypogastric artery is divided and the left side of the pelvis is denuded in a manner similar to that described for the right. The left ureter is freed to its entrance into the bladder.

10. During the various stages of the operation the attempt is made to conserve areolar tissues and nodes in continuity with the uterus and adnexa but this meets with varying success because tissues seem to fall away from each other and groups of nodes and clumps of areolar tissue come away separately during dissection.

The uterus and adnexa are now held firmly upward and forward. This puts the uterosacral ligaments under tension. The peritoneum over the posterior upper portion of the vagina is transected and after peeling it downward

and separating the rectal colon from the posterior vaginal wall downward, the uterosacral ligaments are clamped, divided, and ligated well away from the vagina.

11. Dissection is now carried out about the cervix and vagina and the latter mobilized well downward toward the pelvic floor (Fig. 4). Clamps are placed transversely across the vaginal tube and the latter transected between them in such a manner that at least one-half of the vaginal canal and preferably two-thirds are removed. Bleeding points in the vaginal cuff are ligated. Hemostatic sutures are inserted at each lateral angle of the vaginal cuff.

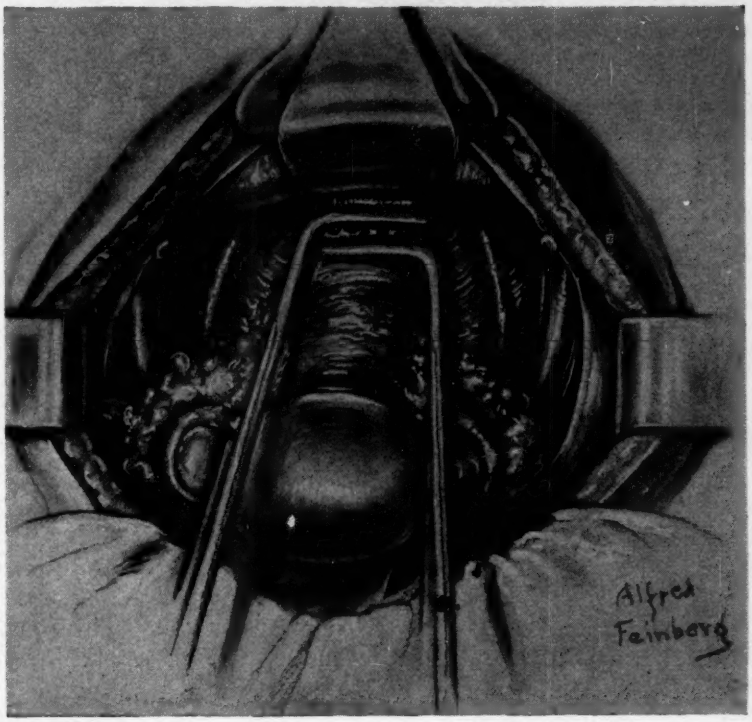


Fig. 4.—Radical dissection of both sides of the pelvis has been completed and right-angle clamps have been applied across the lower vagina. Frequently the lower clamp is not applied, transection of vagina being made below one clamp.

12. The operation is now completed. Reperitonization is not carried out. A wide (4-5 inches) gauze pack is placed in the pelvis, the end being inserted through the open vaginal cuff and the packing placed against the denuded surfaces of the pelvis but principally against the regions of the hypogastric veins.

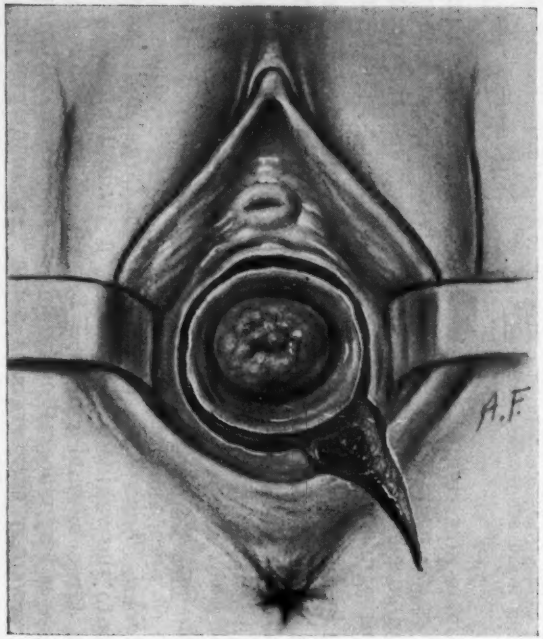
Two soft rubber drains are inserted, one near each ureter and brought out at the inferior angle of the midline incision.

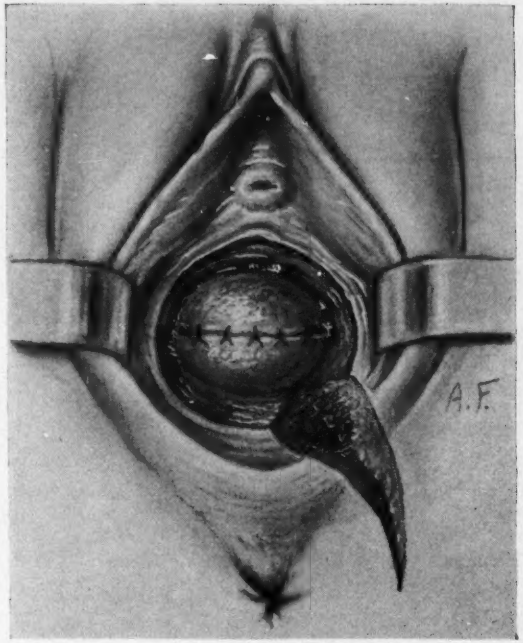
The abdominal wound is closed in the usual manner.

There is, of course, an inlying urethral catheter.

The Vaginoabdominal Operation

Preliminary Vaginal Phase.—When the lesion is large and fungating or appreciable spread onto the vagina has occurred, a vaginal phase is indicated in order to secure a large vaginal cuff and to seal off the lesion to prevent spillage of tumor or spread by maceration during the operation. The fashioning of a vaginal cuff to sew over the cervix is not a new principle but seems to





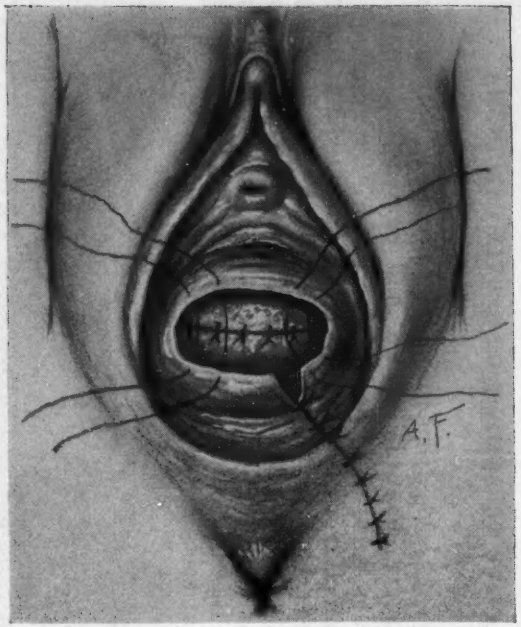


Fig. 5.—Schematic drawing to indicate method of fashioning large vaginal cuff as preliminary perineal phase to radical abdominal hysterectomy. Schuchardt incision to exposure and partial division of left levator ani muscle facilitates wide exposure of the operative field. In practice the carcinomatous cervix is not visualized as a gauze sponge soaked in antiseptic solution is placed over the cervix.

Fig. 6.—The vaginal cuff has been closed over the cervix. Incision into the levator ani muscle has been repaired. The closure over the cervix is made after a gauze sponge soaked in antiseptic has been inserted against the carcinomatous cervix.

Fig. 7.—Repair of Schuchardt incision and partial closure of lower cervical canal. In practice the repair indicated is made after three or four gauze sponges soaked in antiseptic have been inserted against the closed-over cervix.

have been rarely carried out in this country and in the previously described accounts the cuff would seem to have been quite small. In the situation dealt with here a large cuff is envisaged, comprising the upper half to two-thirds of the vagina. The steps in the operation are as follows (Fig. 5):

1. The patient is placed in the lithotomy position. Preoperative urethral catheterization is employed to secure an empty bladder. There is the usual toilet for vaginal operation. Gauze sponges soaked in antiseptic are pressed into the vagina against the carcinomatous cervix.
2. A left lateral incision (Schuchardt) is made, extending from the lower left portion of the introitus downward and outward for a distance of 6 to 8 cm. and deeply to the left levator which is partially divided to secure a wide exposure.
3. The incision is then carried upward in the vagina to a point one-third or one-half way to the cervix. A Kocher hemostat is then applied to the vaginal mucosa above the urethral orifice about half way to the cervix, as a marker.
4. A circular incision is then begun from the inner end of the Schuchardt incision through the entire thickness of the vaginal wall. The bladder is pushed forward and upward off the anterior portion of the upper vaginal cuff. The rectum is separated backward from the posterior aspect of the vaginal cuff. Dissection about the cuff is carried upward but entrance into the peritoneal cavity is not envisaged. Bleeding is encountered from vessels on each side of the cuff and is arrested by ligation.
5. When the cuff is mobilized it is closed by continuous or interrupted sutures tightly inserted, and the gauze sponges placed against the cancerous cervix are sewed in (Fig. 6).
6. Two to four gauze sponges are then inserted against the closed cuff and pressed laterally on each side of the cuff.

The lower vaginal stump may be left open or partially closed by one or two interrupted sutures. The lateral Schuchardt incision is closed by interrupted catgut sutures in layers. The skin is closed with catgut. A catheter is reinserted into the bladder through the urethra (Fig. 7).

The patient is then taken out of lithotomy position, placed in Trendelenburg position, and laparotomy is carried out as described above. In the lower pelvic phases of the operation, the vagina having been transected, this portion of the procedure as described cannot, of course, be carried out. Instead, the palpating index finger seeks the spaces occupied by the sponges inserted against the closed cuff and once this space is entered the sponges are removed and dissection proceeds to liberation of the closed vaginal cuff. As dissection is carried down from above one does not easily enter this space although it would seem easy to do so. It appears that in fashioning the cuff from below one works inside a fascial plane that one remains outside of when proceeding from above downward.

An alternative procedure to facilitate entrance from above into the space that has been created by transection of the vagina and sewing the large cuff over the cervix, is to separate the rectum from the posterior vaginal wall during the perineal phase and perforate the peritoneum of the pouch of Douglas to permit entrance of the tip of the index finger into the peritoneal cavity (Fig. 8). Then, when the operator is working from above during the laparotomy phase, the index finger is inserted into this opening and hooked first under the right and then the left ureterosacral ligament to divide them, thus creating an immediate large opening into the space below the turned vaginal cuff.

All the minutiae of operative procedure cannot be described as certain features, which are important, are acquired with individual experience. Sharp dissection is not considered as efficacious by the author as blunt dissection which

permits a more thorough cleaning away of the areolar tissues and lymph nodes. The areolar tissues which include lymph channels that may contain clumps of tumor cells are to be excised as cleanly and as extensively as possible and it is just as important to have this tissue removed as it is to excise the lymph nodes. If lymph nodes alone are removed, an areolar tissue left behind, one of the principal features of the operation is obviated.

Fig. 8.—Showing method of entrance into space below sewed-over cervix after preliminary vaginal phase (see Figs. 5 to 7). A transverse incision has been made through the peritoneum at the bottom of the pouch of Douglas and the index finger inserted downward to peel the rectum away from the vagina. An opening through the peritoneum in the pouch of Douglas may also be made at the time of the vaginal phase of the operation when the posterior vaginal wall is dissected upward from the colon. The above figure shows the index finger hooked beneath the right uterosacral ligament to free it prior to its transection. In similar manner the left uterosacral ligament is freed before it is transected. Radical panhysterectomy then proceeds as described in the accompanying text.

The ureters cannot be stripped clean of all periureteral tissue as this will result in a high incidence of ureteral slough and fistulas. A web of peritoneum is preserved for the upper portions of the pelvic ureters and a certain quantity of periureteral areolar tissue is preserved about the lower segments that hang freely in their course toward the bladder. Meigs recommends preservation of a small arterial branch to the ureters from the common iliac artery or the hypogastric artery.

In the dissection about the cervix, it is necessary to remain as wide of the cervix as possible and this increases the likelihood of entrance into the bladder or rectal colon or both. The "skeletonization" of the cervix in order to avoid ureteral injury and facilitate excision is to be avoided as this is contrary to the principle of wide excision in cancer surgery. Wide removal of peritoneum is carried out because the subperitoneal areolar tissues contain lymphatic channels that may include tumor cell emboli. Reperitonization is not necessary and no ill effects have ever been noted by omission of this step.

At this point emphasis is again made upon the fallacy of performing a total hysterectomy with excision of parametria, calling the operation a "Wertheim" because cancer of the cervix is present and assuming that a maximal surgical effort has been exhibited (Fig. 9). The latter necessitates the systematic wide excision of lymph nodes and areolar tissue as well as excision of a large portion of vagina (Figs. 10 and 11).

Fig. 9.—Reproduction of drawing accompanying article by Wertheim published in 1912 describing operation commonly referred to as "Wertheim Operation." The procedure is essentially a panhysterectomy with excision of parametria. Note absence of node excision. As indicated in text, this operation does not represent the maximal surgical effort that is feasible.

Postoperative Care.—The general principles of postoperative care after extensive laparotomy apply to these patients. A catheter is placed in the bladder (via urethra) at the close of the operation and left in place for at least five days. It is then removed and the patient catheterized every six hours after voiding to determine residual. When this has fallen to at most 100 c.c. the catheterization is discontinued.

The gauze pack in the pelvis is removed under Pentothal Sodium anesthesia in bed on the day following operation (in 24 hours); if oozing of blood has been greater than normal, it may be left in place for 24 or 48 hours more.

Nothing is permitted by mouth for two or three days, fluid and electrolyte requirements being met by intravenous infusions.

The patients are permitted out of bed on the second or third postoperative day.

Operative Complications

Hemorrhage.—When no large vessels are inadvertently entered a certain degree of blood loss obtains from constant oozing from the denuded surfaces of the lateral pelvic walls. This is compensated for by transfusion. The large vessels which are most likely to be inadvertently entered are: (a) hypogastric

veins, (b) external iliac vein, (c) terminal portion of vena cava, (d) large gluteal veins, (e) veins about the sciatic nerve, (f) veins perforating the anterior sacral foramina, (g) external iliac artery.

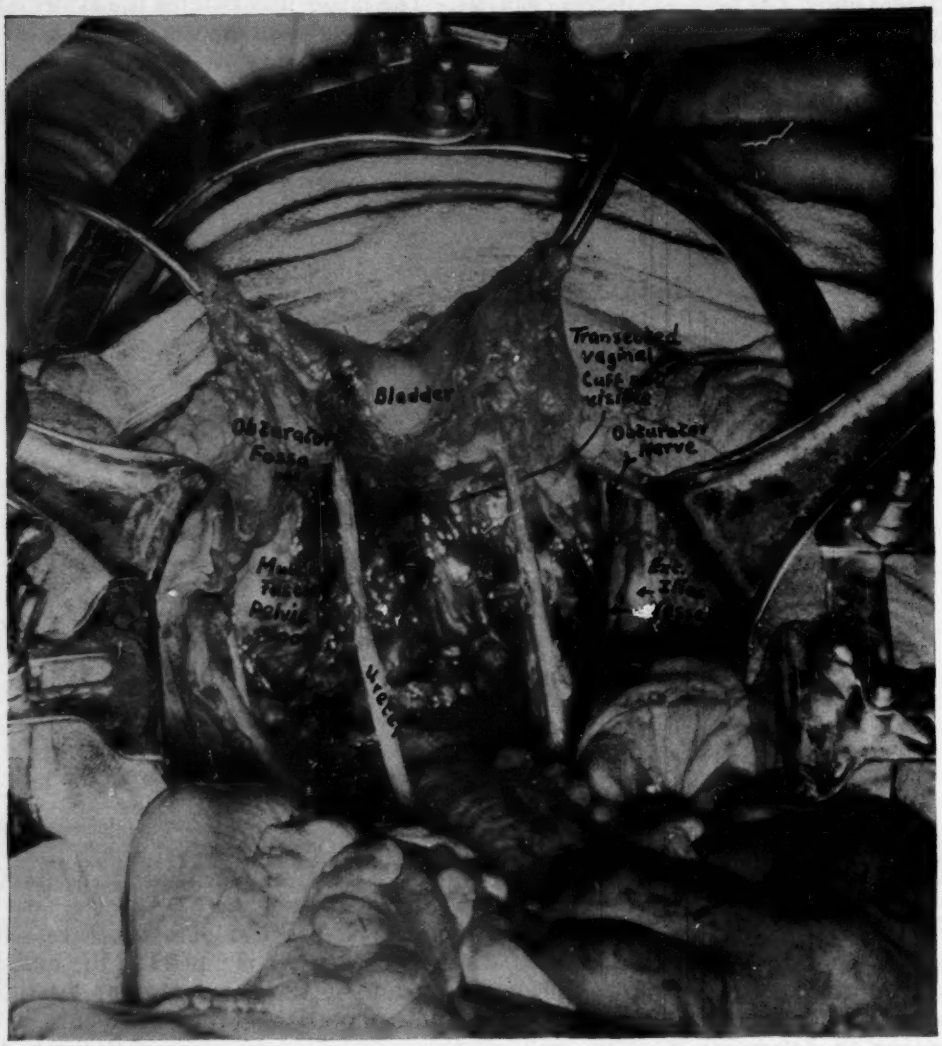


Fig. 10.—Photograph of pelvis at termination of radical panhysterectomy and pelvic node excision. The uterus, adnexa, pelvic peritoneum, contents of the obturator fossae, nodes and areolar tissues over the common and external iliac vessels have been removed. More than half the vagina has been resected. The anterior aspect of the lower pelvic colon has been denuded. The musculofascial pelvic floor is exposed on each side of the rectum and vaginal stump. Some areolar tissue has been preserved about the ureters.

Incision Into the Bladder.—This is not a serious complication. The opening may be repaired with three layers of catgut and a urethral catheter remains in place at least eighteen days following the operation. This may be a longer interval than may be thought necessary but in view of the extensiveness of the hysterectomy and radical excision of the vagina there is less tissue to "bank up" about the bladder and hence the prolonged catheter drainage is deemed advisable. If the opening in the bladder is large it is perhaps preferable to repair it and in addition insert a suprapubic catheter as well as a urethral one. The former remains in situ at least three weeks.

Incision Into Rectal Colon.—This is repaired by two layers of catgut sutures. The deeper one is continuous and the superficial one is of interrupted sutures. With the bowel well emptied prior to operation, the dangers from opening the colon are minimal.

Injuries to the Ureters.—If a ureter is partly divided the continuity is re-established by interrupted fine catgut sutures which pass through all layers except the mucosa. Peritoneum and/or areolar tissue is banked about the site of repair. Prior to repair a ureteral catheter is threaded into the ureter, the upper end passed to just below the kidney pelvis and the lower end into the bladder and then out through the urethra. Or the inferior end may be permitted to remain coiled up in the bladder. This catheter remains in place for at least eighteen days. If the ureter is transected low in the pelvis near the bladder, it is sutured end-to-end, after an appropriate-sized catheter is inserted as above and the bladder "tubulated" about the site of repair (Brunschwig and Pierce). If the ureteral transection is high, the upper end is either tied off or a nephrectomy performed.

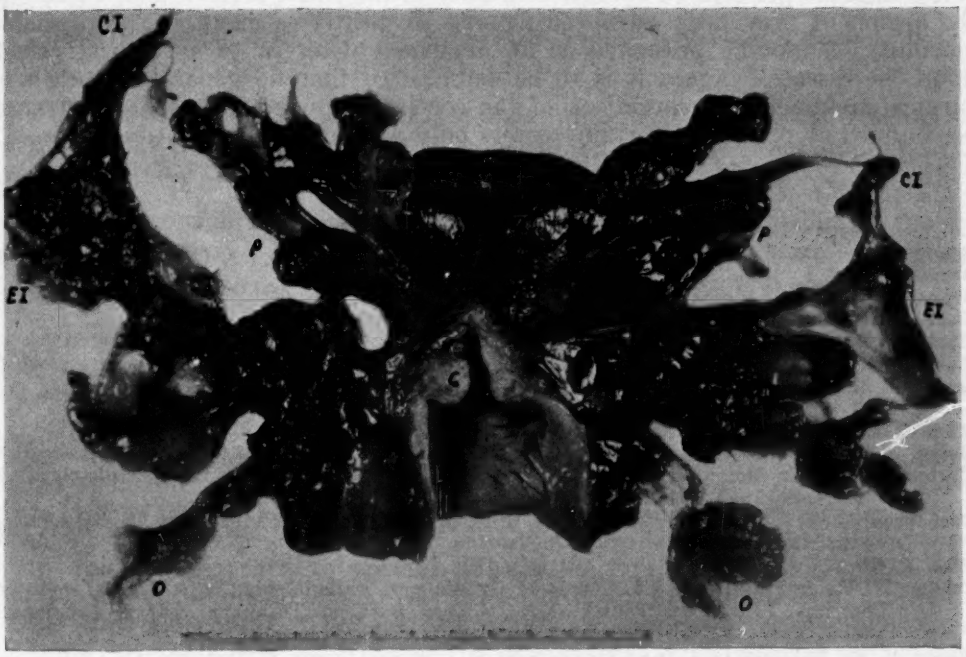


Fig. 11.—Pathologic specimen obtained from radical panhysterectomy with pelvic lymph node excision. C, site of primary carcinoma in cervix; CI, common iliac nodes; P, parametria; EI, external iliac nodes; O, obturator nodes. Note large vaginal cuff, abundance of pericervical and perivaginal tissues. Note also abundance of areolar tissues about lymph nodes. Obviously the specimen was not removed in one piece, but the large groups of nodes and areolar tissues have been placed in proper anatomical relationship to show what is envisaged and accomplished by the operation described in the text.

Comment

Following the above-described radical procedure there is a period of relative bladder atony. The patients do not have a desire to void and accustom themselves to going to the bathroom and voluntarily expelling urine. In the course of a few weeks or longer the sensation of distension of the bladder returns and with this a more normal micturition. In a few patients loss of bladder sensorium has persisted for over two years but the patients have adjusted to this. The vagina is, of course, shortened but the ultimate situation has been

found to vary widely in different patients. For example, in spinsters this has remained shallow. In married women intercourse has been resumed and the vagina deepened to normal proportions; in others it has remained shorter than previously. In still another group, while there had been no intercourse, the healing beyond the short vaginal stump has been such that on pelvic examination a moderately deep "vagina" is revealed.

Results of this operation are not presented at this time because sufficient numbers of patients have not been observed for five years or more. The purpose of the report is to emphasize the point that in order to exhibit a maximal surgical effort a much more comprehensive operation is necessary than total hysterectomy with parametrial excision with a limited vaginal cuff. The latter procedure is not to be recommended for surgical attack upon true (infiltrating) carcinoma of the cervix except perhaps in unusual circumstances.

The positive statement that can be made at this time, however, is that the primary surgical mortality of this extended operation in over 225 patients, *unselected,* who fall into the League of Nations classification I, II, III, and IV, is less than 0.5 per cent (1 operative fatality in the entire series), and, therefore, the argument previously advanced against surgical treatment, i.e., appreciable mortality, cannot be presented as an argument deterent to a surgical attack upon the disease. Again it is to be emphasized that no general advocacy of surgical treatment for carcinoma of the cervix is implied. This problem must be confined at present to certain centers only where special facilities obtain.

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THE CIRCULATING RED CELL VOLUME AND BODY HEMATOCRIT IN NORMAL PREGNANCY AND THE PUERPERIUM*

By Direct Measurement, Using Radioactive Red Cells

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THE purpose of this study was to determine, by direct measurement, the volume of the circulating red cell mass during normal pregnancy and the puerperium.

Direct determinations of the circulating red cell volume during pregnancy have not been made. Indirect measurements, however, have been made many times and the results of numerous volume studies have been reported.

Dieckmann and Wegner,[1] Thomson,[2] McLennan and Thouin,[3] and Caton, Roby and associates,[4] have all measured and reported plasma, whole blood, and red cell volumes during pregnancy.

The studies reviewed agree that there is a progressive increase in plasma volume into the third trimester. Indirectly calculated red cell volumes revealed the same progressive increase. There are differences of opinion, however, as to whether there is a statistically significant reduction in plasma and total blood volume prior to delivery. The length of time for plasma and total blood volume to return to normal also varies in the different reports. No doubt part of the disagreement has been the result of too few determinations on the same individual. The lack of a significant number of postpartum observations, especially late postpartum determinations as compared to the prepartum period, adds to the difficulty in interpreting the gestational data. Perhaps if more investigators had used late postpartum observations for a norm rather than a nonpregnant group, the data might have been better evaluated.

Rather wide variations in results were also reported. These inconsistencies were due in part to the technical limitations of the dye technique. Also, in a small series extreme individual variations, especially when compared to nonpregnant control groups, are of sufficient degree to affect an arithmetic mean. Indirectly calculated red cell volumes are subject to known inherent errors, and in individual determinations this error may be considerable. The use of nonpregnant groups as controls for comparison limits the evaluation of the data in quantitative terms.

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Old and new techniques for simultaneously measuring plasma volume, interstitual fluid, and the circulating red cell mass were used in this study. The results of the plasma volume and extravascular fluid space studies have been reported in a recent paper.[4] In this paper the data derived from red cell volume determinations as measured with red cells tagged with radioactive iron, Fe^{55}, will be described in detail. The relationship between plasma and red cell volume and also the relationship between average venous and body hematocrit will be discussed. Useful interpretation of these relationships has been difficult because of the lack of information on the changes in absolute volume of the circulating red cell mass.

Methods, Materials, and Procedure

The development[5] of the radioactive iron, tagged red cell technique offers an accurate and direct method for measuring the red cell volume. Because the results of the tagged cell technique are independent of variations in hematocrit-plasma ratio throughout the vascular system, a true measurement of the circulating red cell mass is obtained.

In the experiments described in this paper serial volume determinations were made in individuals at regular intervals during pregnancy and the puerperium. Consecutive determinations in individuals tend to minimize errors that inevitably arise when isolated observations are compared with mean values of a control group of nonpregnant women. It was hoped that the data would therefore reveal a trend in red cell volume characteristic of pregnancy.

Twelve patients from the clinic of the Boston Lying-in Hospital cooperated in this study. These women were healthy multiparas and primiparas with no histories of blood dyscrasias. Their diets were adequate and no medication of any kind was taken during pregnancy. One patient had a severe intrapartum hemorrhage. She was the only person who received iron in the puerperium. The usual prenatal advice was given but no attempt was made to restrict the activities of the patients in any manner.

Six to twelve red cell volume, plasma volume, and sodium thiocyanate extravascular space studies were made on each of these patients. A total of eighty red cell volume measurements was completed on the group. Determinations were made at five- to six-week intervals throughout pregnancy. The earliest determination on one patient was two hundred thirty days prior to delivery. An attempt was made to have the last prepartum examination as close to the onset of labor as possible. In the puerperium, volume studies were repeated at the end of the first week in five cases. The last observations were made between the twenty-sixth and sixty-sixth day of the puerperium. With the exception of one mild case of urticaria there were no transfusion reactions.

The radioactive iron method as described by Gibson and associates[5] was used in this study. One hundred c.c. of radioactive, group 0, Rh-compatible blood from prepared healthy male donors were given for each determination. After injection of the tagged cells 15-c.c. samples of venous blood were withdrawn from another vein at ten-minute intervals for fifty minutes. Sampling for all studies necessitated the removal of 100 c.c. of blood. Early in this study the disappearance curve of the dye, T-1824, revealed that mixing time is prolonged during pregnancy. Mixing in the nonpregnant state is complete in ten minutes but during pregnancy at least fifteen minutes are required. The sampling schedules thus employed allowed for complete mixing and provided samples representative of the true ratio of tagged to nontagged cells. After centrifuging, the plasma was removed for plasma volume determinations and the packed red cells were analyzed for radioactivity as previously described.[5]

Analysis of Data

The calculation for the red cell volume follows the procedure as given below and is shown in Fig. 1. A sample V_{s1} is taken to determine the residual activity, R_1, remaining in the patient from the previous determination. This activity has the numerical value of 0 in the initial determination. A volume, V_D, of tagged donor cells was injected and after complete mixing another sample or samples, V_{s2}, were taken to determine the new activity R_2 that resulted from dilution of the donor cells. The actual values of D, R_1, and R_2 represent arithmetic means of from two to five individual samples. Thus the patient's volume at the start of the experiment is:

$$V_{rrx} = V_{rr} - V_D + V_{s1} \quad (1)$$

and the volume at the end of the experiment is:

$$V_{rry} = V_{rr} - V_{s2} \quad (2)$$

By writing a balance equation for the activity in the patient's blood before and after injection of the donor cells it can be found that:

$$V_{rr} = V_D \frac{D - R_1}{R_2 - R_1} \quad (3)$$

and thus, from equation (3) and the known sampling and transfusion volume, the patient's volume V_{rrx} can be determined.

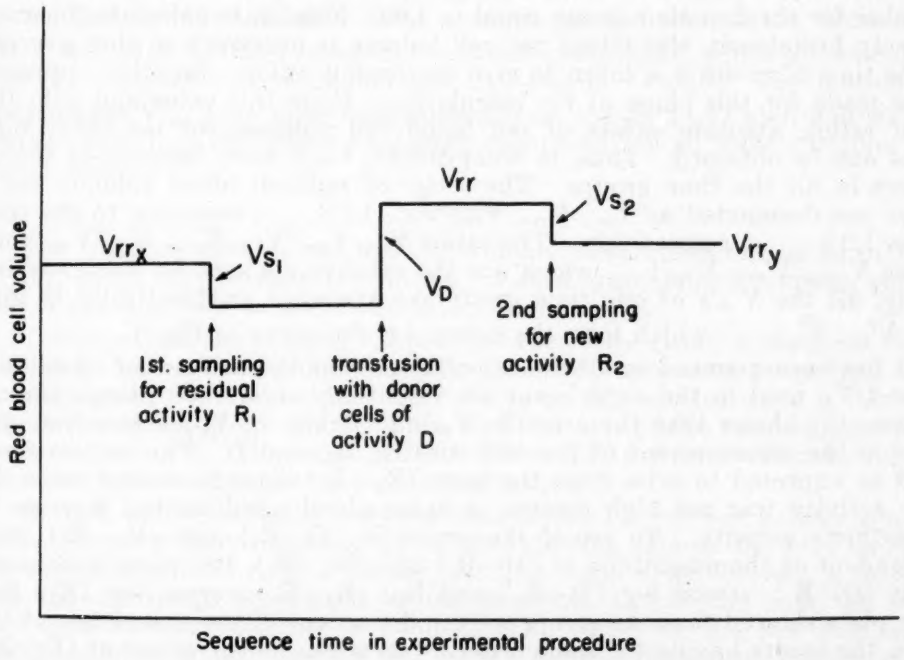

Fig. 1.—Analysis of data.

The decision as to the best manner of presenting these data was difficult. For calculation purposes a forty-day interval had been chosen to represent a time group. An arithmetic mean of the volumes in each time group was considered as one approach, but since the mothers varied quite widely in size and body weight it was thought that such an analysis might lead to excessively large and misleading deviations. A representation of the data in terms of volume per kilogram of original body weight could be criticized on similar

grounds. Presentation, too, in terms of volume per kilogram of body weight at the time of a given determination would be further complicated by the differential increase in body weight that occurs as pregnancy advances.

Because of these variations it was thought that a plot of the data in terms of a relative change in volume, using the volumes of the first group as a reference, would be the most suitable. Thus the relative change in the volumes for each patient could be determined and the relative changes for all patients in one time group could be averaged. To determine a correct relative change, a measurement of the normal volume of the patient is necessary. This determination should be carried out prior to conception but as there were no such measurements the volumes of the first time group were considered to approximate those before pregnancy. The values of the first time group were therefore assigned a value of 1.00. It can be seen that this assumption is reasonable in that the volume of the second time group following delivery is the same as this first one before delivery.

However, since only five of the twelve mothers appear in the first time group, it is impossible to normalize the volume changes for all the patients in the other groups to this first time group. Thus, for calculating purposes, the volumes of time group 3 (where all the mothers appear) were assigned a value of 1.00 and the ratios for the volumes of the other time groups were calculated. The ratios of the various mothers are averaged arithmetically (see below for discussion of this phase) for each time group was renormalized again to make the value for the first time group equal to 1.00. Finally, to calculate the average body hematocrit, the actual red cell volume is necessary so that average volume time of group 3 is taken to give an absolute value. No other approach can be made for this phase of the calculation. From this value and with the use of ratios, absolute values of red blood cell volumes for the other time groups can be obtained. Thus, to recapitulate, V_{rrx}'s were determined for all mothers in all the time groups. The series of red cell blood volumes for a mother are designated as V_{rr1}, V_{rr2}, V_{rr3}, etc., 1,2,3, . . . referring to the time groups 1,2,3, . . . , respectively. The ratios V_{rr1}/V_{rr1}, V_{rr2}/V_{rr1}, V_{rr3}/V_{rr1} then become V'_{rr1}, V'_{rr2}, V'_{rr3} . . . which are the relative changes for each mother. Finally, all the V'_{rr}'s of one time group are averaged arithmetically to give $\overline{V'}_{rr1}$, $\overline{V'}_{rr2}$, $\overline{V'}_{rr3}$ . . . which form the points for the curve in Fig. 1.

It has been assumed in all the calculations that the volumes of blood, V_{s1}, V_{s2}, and V_D used in the experiment are essentially error free. Inspection of equation (3) shows that the error in V_{rr} and finally in V_{rrx} arises from the errors in the measurement of the activities R_1, R_2, and D. The largest error would be expected to arise from the term $(R_2 - R_1)$ since in several cases the donor activity was not high enough to bring about a substantial increase in the mother's activity. To see if the errors in $(D - R_1)$ and $(R_2 - R_1)$ were independent of the magnitude of $(D - R_1)$ and $(R_2 - R_1)$, two plots were made of log $(D - R_1)$ versus log $(D - R_1)$ and log $(R_2 - R_1)$ versus log $(R_2 - R_1)$. These plots showed that the errors were independent of the magnitude of the values, the errors having the same order of variation for all values of $(D - R_1)$ and $(R_2 - R_1)$. Approximately 25 per cent of the volumes showed deviations much greater than the average. Accordingly, two methods of arriving at $\overline{V'}_{rr}$ values were tried: arithmetic and geometric. Assuming that all the volumes had essentially the same error, the arithmetic and geometric means were obtained by weighting the volumes by the inverse square of their standard deviation as calculated from residuals. By use of this method in the latter means, a volume with a large error gives a smaller contribution to the average than does one with a small error. With this method several volumes were shown

to be outweighing others by one to two orders of magnitude. These volumes were then eliminated for calculating purposes to see what their effect was on the averages. Finally, all volumes (about 25 per cent) having a very large error were eliminated to see their effect on the averages. Plots of $\overline{V'_{rr}}$ versus the time during pregnancy were made with the $\overline{V'_{rr}}$'s calculated under the several different conditions described above. All curves revealed the same trend within 10 to 15 per cent. The corresponding arithmetic and geometric means were in all cases essentially the same. This result was interpreted to mean that the deviations in one time group were approximately 15 to 20 per cent. This degree of deviation is compatible with a normal biological spread. Thus there is little choice as to whether a geometric or arithmetic mean is to be used. We chose the arithmetic for the simplicity of these and other calculations. Since all the curves were essentially identical and since it is more difficult to justify the elimination of points from data, especially up to 25 per cent of the points taken, we chose to assume that all the V's were known to the same accuracy. Calculations involving eliminated points yield curves with abrupt changes throughout the plot while the method of our choice results in a rather smooth curve which is consistent with expected physiological changes.

Standard deviations for $\overline{V'_{rr}}$ of each time group were calculated by the method of residuals on the V'_{rr}'s of each time group (except for time group 3 where all the V'_{rr}'s were equal to 1.00 originally and where the actual volumes were used).

Similar calculations have been carried out for the venous hematocrits $\overline{VHCT'}$ and also for the average body hematocrits $\overline{HAU'}$, which are calculated from the experimental red blood cell and plasma volumes. The plasma volume changes $\overline{V'_{pd}}$ have been recalculated from the data of Caton and collaborators.[4] Standard deviations have been calculated for all these variables in a similar manner.

Results

The complete data for all red cell volume calculations are listed in Table I. Also listed are the data for plasma volumes, whole blood volumes, and the ratio of average body to venous hematocrits.

The course of the red cell volumes for the entire group is shown in Fig. 2. The determinations are grouped in periods of approximately forty days, there being six groups before and two after delivery. The circled point is the arithmetic mean of the group and the lines on either side of the mean represent one standard deviation. The range is from 4.50 to 8.47 per cent. The shaded area represents two standard deviations from the mean.

In each patient a statistically significant trend in red cell volume is noted. There is a progressive increase in volume starting late in the first trimester and continuing until term. During the first week after delivery a decrease from the maximum prepartum volume is noted, and in the next ten weeks there is a further decrease in volume. The value for the last postpartum determination is approximately that of the earliest prepartum determination.

Individual variations in the increase in red cell volume are noted, Table II, and these variations are of a degree expected in any normal biological series.

The average increase in red cell volume for the entire group is 1,285 to 1,780 c.c. or a difference of 495 c.c. which is 40 per cent. The increase in volume exceeds two standard deviations about 160 days before delivery. At the end of the first week following delivery there is a decrease of 185 c.c., or 23 per cent. Individual values range from 102 to 570 c.c. During the next four to six weeks

TABLE I. RED CELL, PLASMA, AND WHOLE BLOOD VOLUME MEASURED SIMULTANEOUSLY BY RADIO ION AND DYE TECHNIQUES; AND THE RATIO OF AVERAGE BODY TO VENOUS HEMATOCRIT

CASE NO.	DAYS ANTE OR POST PARTUM	V_D* C.C.	V_{S1}* C.C.	V_{S2}* C.C.	D* CPM/C.C.	D*	R_1* CPM/C.C.	R_1*	R_2* CPM/C.C.	R_2*	VRR_x* C.C.	VPD* C.C.	HCT. V* 0/0	VWRD* C.C.	HCT. A 0/0	$R = \frac{\text{HCT. A*}}{\text{HCT. V}}$
5	–159	43.4	0	29.8	871	3.5			25.4	.03	1472	2810	41.4	4282	34.3	.828
	– 93	41.1	8.3	20.7	1345	5.0	27.2	1.00	60.6	3.24	1587	3600	36.3	5187	30.6	.843
	– 53	43.0	8.9	21.9	6257	20.3	41.9	.98	193.8	3.55	1726	4400	33.8	6126	28.2	.834
	– 11	40.3	8.3	23.3	1570	10.0	235.0	6.45	263.6	9.58	2008	4400	33.8	6408	31.3	.926
	+ 7	49.0	8.3	17.9	694	4.7	252.5	6.22	272.0	3.56	1054	3000	30.9	4054	25.9	.838
	+ 66	43.0	7.9	23.1	1767	33.2	191.0	.81	239.0	2.99	1377	2730	36.1	4107	33.6	.931
6	–172	38.7	0	25.5	877	10.5			24.2	2.64	1486	2800	39.9	4296	34.8	.872
	–131	38.8	9.7	23.5	1910	40.0	40.6	18.2	67.3	1.44	1601	3366	37.7	4967	32.2	.853
	– 90	40.5	9.3	21.6	852	4.8	49.8	1.10	65.6	1.07	1909	4100	34.7	6030	32.0	.922
	– 49	39.8	8.5	21.9	1787	66.7	79.7	1.00	111.5	2.32	2094	4160	32.5	6255	34.0	1.045
	– 3	49.0	9.4	23.1	645	17.3	95.0	2.06	108.0	2.17	1740	3460	35.2	5200	33.5	.952
	+ 45	43.0	10.3	24.3	6303	237.5	77.0	1.78	288.0	17.6	1222	2710	38.2	3832	29.3	.768
7	–208	41.5	0	28.2	994	46.5			34.6	.20	1138	2154	39.2	3292	34.6	.881
	–161	39.0	9.9	20.9	1730	50.0	33.7	.10	63.5	.69	2181	2566	35.3			
	–123	39.0	8.5	20.1	938	2.0	71.0	3.55	97.4	3.42	1300	3080	32.2	4380	29.6	.918
	– 82	25.7	8.0	21.0	1567	56.1	104.0	.94	136.0	1.67	1157	3480	31.1	4637	25.2	.808
	– 41	38.5	6.5	12.1	1343	13.3	120.2	1.84	151.0	3.61	1473	3750	28.1	5223	28.2	1.005
	0	45.5	8.0	22.7	1637	23.3	129.0	1.97	186.0	4.63	1013	3300	32.2	4313	23.5	.738
	+ 26	41.0	9.3	26.2	6350	17.3	188.5	11.7	394.0	2.85	1153	2180	37.4	3334	34.7	.928
8	–132	46.0	0	26.0	6830	20.0			261	2.59	1154	2800	37.6	3954	29.1	.775
	– 91	41.4	9.4	21.6	8260	74.5	269	5.00	496	6.28	1433	3110	35.6	4543	31.5	.885
	– 50	41.0	8.6	18.7	6927	188.8	377	3.12	574	8.89	1753	3315	32.5	5063	34.5	1.063
	0	44.0	9.1	19.7	2540	138.9	746	14.8	782	19.2	1580	3060	35.7	4640	34.0	.953
	+ 7	41.2	9.4	21.6	1987	31.7	577	25.1	658	27.8	1183	2640	35.5	3822	30.9	.870
9	–197	43.5	0	23.2	6900	70			247	2.64	1167	2560	36.9	3727	31.3	.850
	–155	42.0	9.2	22.7	8360	80	247	2.00	478	4.74	1407	3310	35.0	4717	29.8	.853
	–113	41.5	8.4	21.4	7307	125.8	370	3.05	514	7.65	1957	3520	33.3	5477	34.9	1.076
	– 85	40.5	8.0	18.9	8453	113.5	656	6.08	849	9.96	1618	4410	29.9	6028	27.9	.898
	– 29	40.5	7.0	18.2	1903	23.4	713.5	.50	750	14.04	1301	4660	27.0	5961	21.9	.812
	+ 13	41.2	8.0	20.3	6830	111.5	650	7.26	794	9.4	1752	4175	30.0	5927	29.5	.985
11	–148	36.9	0	16.1*	994	15.5			20.1	.69	1793	3973	35.9	5766	31.1	.865
	–111	28.6	7.8	20.1	1275	5.0	17.8	.60	41.8	.47	1479	4630	32.3	6110	25.2	.778
	– 78	40.0	8.9	12.3	1040	15.3	33.0	2.43	57.5	.32	1719	5285	31.7	7004	24.4	.771
	– 39	43.5	8.1	20.1	1653	208.5	62.4	1.18	103.5	9.39	1705	5425	29.4	7130	23.9	.813
	– 4	43.2	8.6	21.4	646	6.1	85.9	1.18	96.0	.46	2405	4975	32.5	7380	32.5	1.000
	+ 7	42.8	10.1	27.2	6963	112.6	82.8	.84	257.0	1.40	1897	3500	37.8	5391	35.2	.932
	+ 65	39.4	8.5	17.3	6757	109.8	270.0	14.7	403.0	6.41	1884	3410	34.6	5295	35.6	1.028

12	−215	43.0			7615	135			281	3.60	1124	2440	37.0	3564	31.5	.853
	−180	42.5	8.5		8470	70	267	5.50	592	19.1	1037	2714	35.4	3751	27.6	.780
	−138	39.5	8.4		7163	92.1	384	4.44	566	14.8	1439	3110	34.2	5549	26.4	.772
	+ 30	33.7	8.4		6023	114.7	425	12.3	572	9.73	1256	2680	33.7	3936	31.9	.945
13	−200	43.0	0	18.0	836.5	80.5			26.8	.73	1302	2930	39.6	4232	31.7	.800
	−140	38.8	10.5	22.3	1323	23.4	29.3	2.00	57.7	1.12	1887	3290	37.5	5277	35.8	.955
	−104	39.1	8.1	21.3	6937	165	44.8	1.07	223.8	4.36	1704	3510	34.4	5214	32.6	.948
	− 68	37.8	8.4	21.8	1460	17.3	233.8	3.43	255.8	3.02	2056	4400	32.5	6456	31.8	.980
	− 26	44.5	7.8	15.6	6620	30	199.7	1.98	356.7	10.3	1778	4200	35.2	5979	30.9	.878
	− 1	44.6	8.6	23.8	1767	18.6	335	7.67	354.6	7.65	2984	3710	36.5	6694	44.7	1.175
	+ 30	43.5	9.0	26.7	5820	47.3	317.5	4.67	455.2	4.62	1570	3080	38.7	4650	33.7	.870
14	−167	43.0	0	23.3	650	71.5			26.0	9.33	1297	3050	38.6	4347	29.9	.774
	−125	41.0	9.1	22.2	1690	20.0	31.1	.65	69.0	2.04	1718	3410	35.1	5128	33.5	.951
	− 83	44.5	8.0	21.7	1630	50.0	59.0	1.37	94.6	1.26	2113	3880	34.5	5993	35.2	1.020
	− 70	39.5	8.5	18.3	1447	32.8	82.1	1.32	119.0	.74	1419	4825	32.2	6244	22.7	.705
	− 30	41.0	9.9	22.6	7043	159.3	98.5	1.53	256.0	2.78	1769	4540	32.8	6309	28.1	.857
	+ 61	46.5	9.8	23.0	6440	87.2	205.0	11.3	420.0	8.26	1213	2760	40.7	3974	30.5	.748
15	−233	39.5	0	25.8	1750	100			44.1	1.47	1526	2850	39.6	4375	34.8	.878
	−189	41.0	9.5	23.1	1650	16.8	51.9	.10	93.7	1.50	1519	3380	36.5	4899	31.0	.848
	−147	44.5	9.2	21.6	1583	12.0	72.3	1.22	123.0	6.61	1310	3720	34.6	5030	26.0	.752
	− 97	41.0	8.6	22.1	1510	15.3	109.0	2.24	142.0	.97	1708	3600	35.0	5308	32.2	.915
	− 55	42.0	9.3	23.9	6650	91.6	118.0	2.38	282.0	3.57	1812	3960	33.7	5773	31.4	.931
	− 18	41.5	7.7	22.2	6673	69.6	264.0	24.1	405.0	6.00	1836	4000	33.3	5836	31.7	.952
	0	40.5	9.1	21.6	6417	120.0	441.0	22.7	548.5	16.1	1879	3260	34.1	5240	35.9	1.052
	+ 1	40.0	9.0	24.7	6587	66.4	546.0	22.0	717.2	4.23	1734	2950	36.5	4684	37.0	1.015
	+ 3	39.0	8.4	23.7	5890	49.3	645.0	18.1	746.6	21.9	1869	3340	35.4	5209	35.8	1.010
	+ 6	37.0	9.1	22.2	5703	16.6	760.0	9.81	851.0	43.7	1777	3520	34.4	5297	33.6	.977
	+ 30	44.0	9.4	19.8	6176	37.1	939.0	37.0	1045.0	14.4	2365	2710	37.6	5075	46.6	1.235
16	−196	40.0	0	25.1	2747	335			95.3	1.05	1115	2960	35.6	4075	27.4	.770
	−161	40.5	10.2	21.8	1143	3.3	42.8	.71	75.5	.79	1335	3290	34.9	4625	28.9	.828
	−120	43.5	8.6	21.7	1597	20.3	88.5	13.7	126.2	1.64	1315	3420	34.2	4735	27.8	.813
	− 78	38.0	7.5	20.3	1357	12.0	118.0	2.24	153.0	2.50	1420	3525	32.2	4945	28.7	.892
	− 43	40.7	9.4	23.0	1853	6.7	134.0	2.68	164.0	1.48	1995	3620	33.5	5615	35.6	1.060
	− 6	46.5	9.7	23.6	6390	10.0	157.0	2.64	330.0	12.1	1718	3580	34.5	5298	32.5	.942
	+ 42	40.1	10.3	24.4	6767	57.0	345.0	33.4	531.0	6.50	1350	2665	37.3	4015	33.6	.900
17	−200	39.2	0	24.5	1740	30.0			46.4	.87	1431	3580	36.4	5011	28.6	.785
	−165	44.5	8.4	22.0	890	12.2	36.6	1.33	58.5	.74	1703	3615	34.1	5318	32.0	.938
	−126	40.5	8.8	20.4	1877	46.7	73.1	2.02	113.0	1.73	1791	4200	32.3	5991	29.9	.925
	− 85	49.0	8.0	19.1	667	8.1	99.5	.74	121.0	1.82	1250	4150	32.3	5400	23.1	.715
	− 44	44.0	8.6	22.3	1640	55.7	96.3	1.26	135.0	.78	1701	4325	31.5	6026	28.2	.895
	− 16	43.5	7.7	20.8	6237	83.3	127.0	3.61	281.0	1.94	1696	4600	29.8	6296	26.9	.904
	+ 7	43.0	4.9	14.0	6450	66.6	270.0	2.83	580.0	33.4	818	3580	21.2	4398	18.6	.878
	+ 33	41.5	7.3	23.5	6527	53.7	333.0	8.14	490.0	5.83	1616	3200	35.0	4816	33.5	.958

*See Fig. 1.
V_D = Volume of donor cells transfused
V_{S1} = Volume of cells in first sampling for residual activity, R_1
V_{S2} = Volume of cells in second sampling for new activity, R_2
D = Total activity in total donor cells
R_1 = Residual activity
R_2 = New activity following transfusion of donor cells

V_{rrx} = Red cell volume prior to beginning of determination
V_{pd} = Plasma volume by dye method
Hct. V. = Venous hematocrit
V_{wrd} = Whole blood volume (sum of V_{rrx} + V_{pd})
Hct. A = Average body hematocrit
R = Hct. V = Ratio of average body to venous hematocrit

there is a further decrease in volume to approximately 450 c.c. below the prepartum maximum. The range of decrease in individual volumes is from 80 to 566 c.c. At the last postpartum determination, 60 days following delivery, the average volume for the group is almost identical to the earliest prepartum volume. This last postpartum volume is within two standard deviations.

The course of plasma volume is included in Fig. 2 to show the relationship of changes in red cell to plasma volume and also of changes in whole blood volume. The increase in plasma volume at the average maximum, about 60 days before delivery, is 55 per cent and is approximately 15 per cent greater than the increase in red cell mass. This degree of hemodilution is consistent with hematocrit and other changes previously noted in the blood during pregnancy. Sixty days following delivery the plasma volume is within three per cent of that determined at the end of the first postpartum week, and each value is within two standard deviations. The individual variations in plasma volume are similar to those noted for the red cell volume.

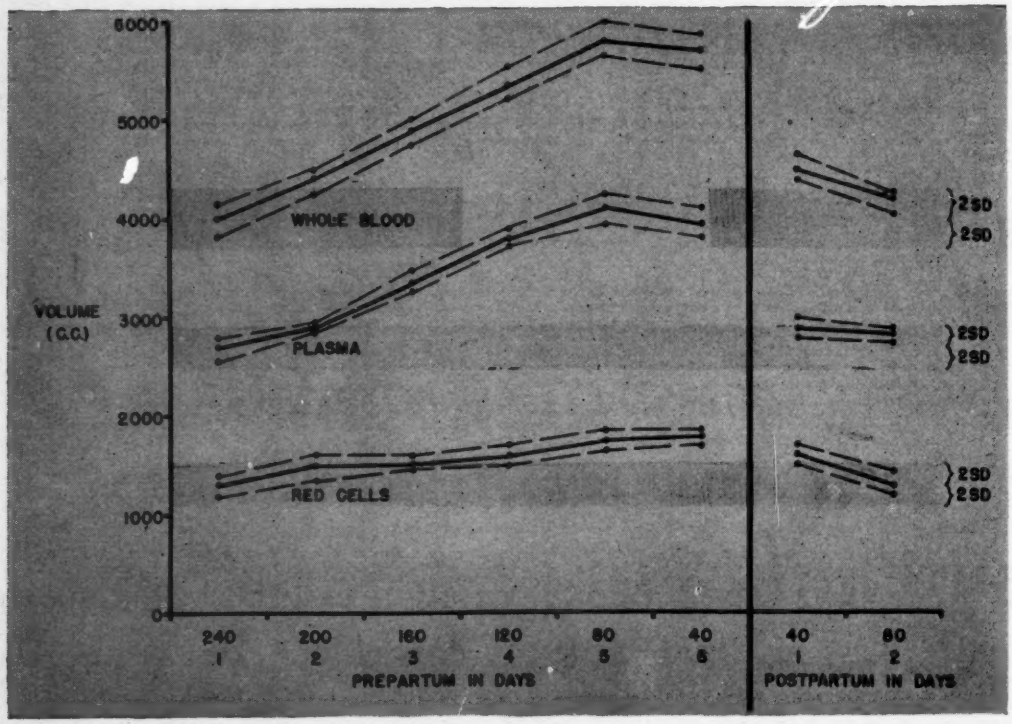

Fig. 2.—Red cell, plasma, and whole blood volumes during normal pregnancy and the puerperium.

The solid lines are the means of red cell, plasma, and whole blood volumes. The broken lines running parallel to the solid lines represent one standard deviation. Each shaded line represents plus or minus two standard deviations from the mean. Standard deviations were calculated by the method of residuals and for small samples.

The net result, illustrated in Fig. 2, of the changes in red cell and plasma volume is a great increase in whole blood volume. The average increase of whole blood for the group is approximately 1,800 c.c., or 45 per cent. The maximum volume is noted 60 days before delivery. However, whole blood volume follows the trend of plasma volume so that in an individual a maximum volume may occur 68 to 5 days prior to delivery. The increase in volume exceeds two standard deviations 180 days before delivery.

Whole blood volume decreases 22 per cent during the first postpartum week, and this value exceeds two standard deviations. Sixty days after delivery the volume is within five per cent of the initial prepartum determination. This value is within two standard deviations.

The changes in venous hematocrit for the group are shown in Table II. A mean decline from 39.4 to 32.0, or 15 per cent, occurs. A minimal increase in hematocrit occurs prior to delivery and this increase is accentuated by labor.

The changes in average body hematocrit, also shown in Table II, reveal a similar but less marked trend, the values ranging from 32.2 to 29.5, or a decrease of 8.4 per cent.

TABLE II. MEAN VALUES AND STANDARD DEVIATIONS OF RED CELL, PLASMA, AND WHOLE BLOOD VOLUMES; AVERAGE BODY AND LARGE VESSEL HEMATOCRIT AND THEIR RATIOS

		DAYS ANTE PARTUM						DAYS POST PARTUM	
		240-200	199-160	159-120	119-80	79-40	39-0	1-39	40-80
PERIOD		1	2	3	4	5	6	7	8
Vrr_x	c.c.	1285	1475	1515	1615	1725	1780	1595	1335
S. D.	%	8.10	8.47	4.50	5.32	4.87	5.02	7.92	6.82
Vpd	c.c.	2695	2900	3374	3790	4120	3950	2910	2850
S. D.	%	4.2	1.97	3.63	2.63	3.9	3.41	3.46	3.64
Vwrd	c.c.	3980	4375	4889	5405	5845	5730	4505	4185
S. D.	%	3.86	3.15	2.86	2.44	3.10	2.81	3.58	3.30
Het L	%	39.4	37.1	35.2	33.0	32.0	32.3	35.8	36.4
S. D.	%	2.77	0.80	2.09	1.41	1.98	1.63	3.09	5.93
Het A	%	31.9	32.3	31.2	30.5	30.0	31.0	33.6	32.9
S. D.	%	8.97	9.04	5.33	5.85	5.77	5.75	8.69	7.57
$R = \frac{\text{Het A}}{\text{Het L}}$		.810	.870	.885	.923	.937	.960	.938	.902
S. D.	%	9.39	9.07	5.73	6.02	6.10	5.98	9.22	9.62

Comment

The data presented indicate that a definite increase in the circulating red cell volume occurs during normal pregnancy. The progressive increase in values for the red cell volumes observed in this series from early pregnancy to term is statistically significant and leaves no doubt as to the reality of the increase. The same can be said for the increase in plasma and hence whole blood volume.

Absolute red cell volumes are related to body mass but no attempt is made to correlate volume changes with body weight as pregnancy advances. A direct relationship does exist between body size and red cell volume in the nonpregnant state, but during pregnancy as body size and weight each increase, water retention accounts for a proportionately greater increase in weight than protoplasm. Therefore, any correlation of red cell volumes during pregnancy with mass will result in misleading interpretations.

In the early puerperium, in the absence of abnormal blood loss at delivery, total blood volume declines markedly but not to normal. This decrease is almost entirely due to plasma volume as the red cell volume has not decreased appreciably. It is of interest that the red cell volume does not return to normal until the second month after delivery. The gradual decrease in red cell volume during this period cannot be explained by blood loss but could be the result of an increased rate of destruction of circulating red cells or of a slight depression in bone marrow activity.

The data make possible the calculation of the demand on maternal iron to provide for the increase in red cell volume. If it is assumed that the red cell has a normal life span during pregnancy and that hemoglobin iron is normally

re-utilized, the increase in new hemoglobin iron requirement can be met only by an increasing absorption of and re-utilization of iron in the bone marrow. Since the increase in the red cell mass is a linear function of time, as are the fetal needs, the absolute iron requirement will progressively increase throughout pregnancy. Thus at no time during pregnancy is there any sudden demand on maternal iron reserves.

The iron demand of 500 mg. for new red cells in this group of normal women was satisfied on a diet not supplemented with iron. Complete iron metabolism studies on a larger group of women resulted in similar conclusions.[6]

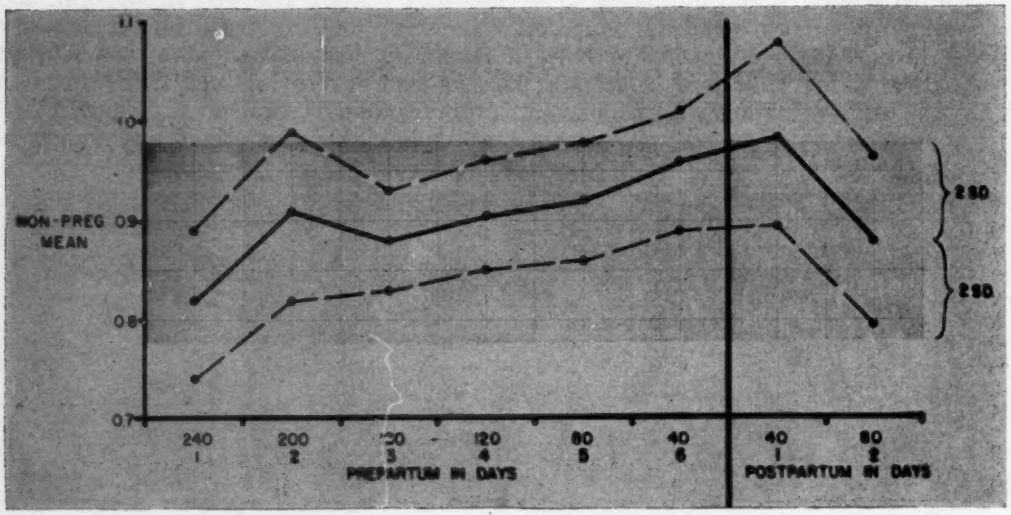

Fig. 3.—The ratio of average body to venous hematocrit during normal pregnancy and the puerperium.

The solid line is the mean ratio. The broken lines represent one standard deviation from the mean. The shaded area represents two standard deviations from the mean.

Standard deviation for significance is plotted from time group 3 where all the patients studied first appear. Standard deviation was calculated using the method for small samples.

Body hematocrit is the average cell to plasma ratio of the total circulating blood. The ratio of the body hematocrit to the large vessel hematocrit is dependent upon the distribution of whole blood between the large vessels and capillaries.[7] In the nonpregnant state about 20 per cent of the total blood volume is circulating in the capillaries and 80 per cent is in the large or transport vessels. With blood distributed in this proportion, the ratio of body to venous hematocrit is 0.8. The hematocrit of capillary blood is lower than the body hematocrit because of the smaller caliber of the vessel while the larger vessels have a higher cell-plasma ratio or hematocrit. Therefore, if more than 20 per cent of the total blood volume is in the capillaries, the ratio of body to venous hematocrit will fall. Conversely, a redistribution of blood which results in more than 80 per cent in the higher hematocrit large vessels will be reflected by an increase in the ratio of body to venous hematocrit. Therefore, the ratio between body and venous hematocrit is an index of distribution of blood in the vascular bed.

It is of interest to compare the ratios in this group of pregnant women with those of the nonpregnant state. The ratios of these values are shown in Fig. 3. Both body and venous hematocrit decline during pregnancy but the decline in venous hematocrit is twice as great as that of the body hematocrit. This difference in degree of decline, 15 per cent in the venous hematocrit and only 8 per cent in the body hematocrit, results in the increased ratio.

Although two standard deviations are not exceeded, except for the observations in the early puerperium, it is felt worth while to offer an interpretation of these hematocrit changes. The data do reflect a definite trend. The progressive increase in the ratio as pregnancy advances suggests that a redistribution of blood occurs and that the greater portion of the new blood volume is accommodated by the large transport vessels rather than equally distributed, 80 per cent and 20 per cent, with the enlarging capillary bed. In the early puerperium where the value exceeds two standard deviations, the ratio is the highest. The increasing ratio following delivery can be interpreted as reflecting the loss of a relatively greater capillary than large vessel flow. In the absence of any marked decrease in whole blood volume the change in the hematocrit ratio must follow changes in the vascular bed. What these vascular bed changes are and how delivery and the early puerperium result in a predominant loss of capillary flow can be determined only by future studies. Our data suggest that such changes possibly occur.

Conclusions

1. An increase of approximately 495 c.c. of red cells, or 40 per cent, occurs during normal pregnancy.

2. The increase in the circulating red cell mass is significant and exceeds two standard deviations 160 days prior to delivery.

3. At the end of the first week in the puerperium the red cell volume increase still exceeds two standard deviations. The volume of the red cell mass returns to normal nonpregnant limits approximately 60 days following delivery.

4. Whole blood volume increases by approximately 1,800 c.c., or 45 per cent, during normal pregnancy.

5. Body hematocrit and large vessel hematocrit each decrease during pregnancy. The average decrease in venous or large vessel hematocrit is 15 per cent, while body hematocrit decreases only 8.4 per cent.

6. The ratio between body hematocrit and venous hematocrit increases during normal pregnancy. The high ratio suggests that a relatively greater part of the blood volume is accommodated by the large vessels rather than the capillary bed.

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STUDIES ON SURVIVING HUMAN PLACENTAL TISSUE
III. THE TOXICITY OF PLACENTAL PERFUSATES

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ECLAMPSIA is the toxemia of pregnancy par excellence, but we are so far from an essential understanding of it that we do not know if it is truly a toxemia or even whether it is indeed a specific disease. The cause is unknown, the clinical manifestations are varied, and the pathology is inconstant. Many attempts have been made to produce the syndrome in animals, and many of its features have been reproduced. However, the interpretation of these experiments is difficult for at least two reasons. First, eclampsia does not seem to occur spontaneously in animals other than the pregnant woman, and we therefore do not know what form experimental eclampsia might take. Second, human eclampsia is so unpredictable in its clinical signs and pathology that one cannot set up any definite criteria which must be fulfilled for the recognition of its experimental production. For all we really know, Wooldridge[14] may have produced experimental eclampsia three-quarters of a century ago (1887), when he injected "tissue fibrinogen" into dogs. Schmorl,[10] who repeated his work, thought that he had done so.

Attention has been centered upon the placenta as the source of the "elusive eclamptic toxin," and reasonably so because the prevailing opinion is that the disease is specific to pregnancy, and has a high incidence in hydatidiform mole where there is no fetus. Many investigators have studied the toxicity of placental extracts, autolyzates, and press juices. The most recent work is that of Schneider,[11] who has identified the toxic substance in saline extracts of the placenta as thromboplastin. Sublethal doses of the extracts, given intravenously, produced focal necrosis in the livers of about 30 per cent of his mice.

Beker[2] has correlated a deficient uterine blood supply with many of the predisposing factors in eclampsia, such as primigravidity, multiple pregnancy, hypertensive disease, diabetes, etc. Page,[9] and, independently, Bastiaanse[1] have suggested that placental or gravid uterine ischemia may be the factor which leads to the release of toxic substances. Page has correlated a large number of clinical, chemical, and anatomical observations which are in consonance with this hypothesis.

We were stimulated by Page's paper to undertake the present study. In a previous paper,[5] we reported that slow perfusion (artificial ischemia) of surviving human placental tissue resulted in the release of an antidiuretic substance which had no effect upon the chloride excretion. No pressor substance could be found in acute experiments.

It is our purpose now to report experiments in which we have given repeated intravenous injections of placental perfusates to rabbits and dogs. The "ischemic" perfusates were found to be toxic, and the toxic factor does not seem to be either thromboplastin or the euglobulin described by Smith.[12]

Material and Methods

With very few exceptions, placentas from apparently normal patients were used. The placentas were obtained only from patients who came to cesarean section with intact membranes, because absolute sterility is essential in the culture of organs. As previously described,[5] a fetal artery supplying a single cotyledon was cannulated, and the blood washed out with Tyrode solution. The cotyledon was then placed in the Lindbergh pump for perfusion. Aseptic and antiseptic (Dakin solution) technique was used throughout.

The perfusion medium was 200 to 300 ml. of 15 to 30 per cent human serum in Tyrode solution, to which phenol red had been added as an indicator of the pH, which was adjusted to 7.4. The gas mixture was 80 per cent oxygen, 15 per cent nitrogen, and 5 per cent carbon dioxide, except where otherwise noted. All perfusions were done with a pressure of about 90/50 mm. Hg in the organ, and the pulsation rate was 86 to 90 per minute. The temperature was 37° to 38° C. In general, we followed closely the details of technique as outlined by Carrel and Lindbergh.[3]

In the experiments on artificial placental "ischemia," the perfusion was considered to be slow enough if the perfusion medium bleeding from the cotyledon showed a slight drop in pH; this fluid can be seen in the organ chamber and in the central portions of the pump. The rate of perfusion was reduced by trapping an air bubble under one of the screens in the feed tube. The control experiments were those in which the placental cotyledon was perfused at a much greater rate.

It should be emphasized that we have perfused the fetal vessels, and that as the perfusate bled from the vein it washed a portion of the maternal surface of the cotyledon's basal plate. The surfaces of the villi, normally bathed in maternal blood, therefore made very little if any direct contribution to the perfusion medium. The hypoxia consequent to the very slow perfusion in the ischemia experiments may have increased cell permeability enough to allow some substances to get into the fetal vessels.

Although the perfusates were sterile, they were filtered through Berkefeld or Seitz filters when removed from the pumps. This was merely a matter of convenience in transferring the perfusates to sterile containers.

The perfusates were injected intravenously at four-hour intervals. In 25 immature, nonpregnant rabbits (about 14 weeks old), the dose was 20 ml. at each injection. In the 12 dogs, 50 ml. doses were given.

Blood pressures were estimated in some of the rabbits, using the method of Grant and Rothschild.[7] Blood pressures in dogs were not determined, for want of facilities. Protein in urine and ascitic fluids was determined by the tungstic acid precipitation method and the Kjeldahl micromethod. Blood nonprotein nitrogen was determined by Wong's persulfate method.[13] If the animals did not die spontaneously, they were killed by air embolism from three to thirty hours after the last of a series of injections of perfusate. Autopsy tissues usually were obtained within minutes after death, and were fixed in formalin; sections were stained with hematoxylin and eosin. Usually the kidney tissue was fixed in Zenker's solution and the sections stained with azancarmine.

Many observations are incomplete, for rather special reasons. Injections were given at four-hour intervals, around the clock, which necessitated taking the animals home at night. Many of them died after three or four injections, and facilities at home did not permit of blood pressure readings, for instance. As it was, all traditions of the train commuter's traveling light were disregarded. Another difficulty was met in the animal lovers, in consideration of whose delicate feelings we did nearly all of the dog work in the clandestine depths of our cellar at home.

Results in Rabbits

The rabbit experiments may be divided into four groups:

A. Three rabbits were injected repeatedly with perfusion medium which had not been used in perfusing tissues. Two rabbits showed no effects grossly or histologically after thirteen and twenty-three injections. The third died in convulsion after thirteen injections. This last rabbit had an initial proteinuria of 5.3 Gm. per liter, which increased slightly. At autopsy, there was a slight excess of fluid in the abdominal cavity. Microscopically, the liver showed fatty degeneration; the kidney slides showed subacute glomerular nephritis.

B. Two rabbits were injected with 760 and 260 ml., respectively, of perfusates from experiments in which the placenta was perfused in an atmosphere of 95 per cent nitrogen and five per cent carbon dioxide. There was no obvious effect, grossly or histologically, except for a blood nonprotein nitrogen of 86 mg. per 100 ml. in the first rabbit.

C. Eight rabbits were injected with large amounts of perfusates from adequately perfused placentas.

D. Twelve rabbits were given "ischemic" perfusates. These last two groups will be discussed below.

Convulsions and Death.—Six of the twelve rabbits receiving injections of perfusate from artificially "ischemic" placentas were seen to die in convulsion. This always occurred at least an hour after the last injection, and followed from three to six injections, that is from nine to twenty-five hours after the initial injection.

Of the eight rabbits injected with perfusates from placentas which had been perfused rapidly, three died in convulsion; two of these had received thirteen injections, and one had six.

Obviously, the perfusates from the very slowly perfused placentas were much more toxic than those from adequately perfused placentas (flows of twenty to forty ml. per minute). No significance is attached to the convulsions, which are unremarkable in rabbits.

Proteinuria.—Of the rabbits receiving "ischemic" perfusates, two were so markedly oliguric that no urine could be obtained; one other died after three injections, and the bladder was empty at autopsy. The other rabbits of this group had proteinurias ranging from 2.6 to 13.8 Gm. per liter, with one at the remarkable level of 57.6 Gm.

The rabbits injected with perfusates from placentas adequately perfused also showed proteinuria which typically was 2 to 4 Gm. per liter, with one at 13.5 Gm. Many of the rabbits had proteinurias ranging up to 1 Gm. per liter before the injections were begun.

The injection of foreign protein (human serum proteins of the perfusion medium) might be expected to result in increased proteinuria. However, the rabbits injected with "ischemic" perfusates showed a much more profuse proteinuria than did the others. Associated with the proteinuria were red blood cells and granular casts. These were seen in most rabbits, but especially in the animals given the "ischemic" perfusates.

Blood Pressure.—We are not satisfied that our measurements of blood pressure, made by the method of Grant and Rothschild, are reliable, for one can see the ear artery constrict and dilate during and after the determinations. When the artery is constricted, the readings will be too low. Whatever errors there may be in our determinations would be in underestimating the blood pressure. Our initial and control readings were all in the range of 70 to 90 mm., as reported by Grant and Rothschild.

In six rabbits receiving "ischemic" perfusates, the pressures have ranged from 85 to 160 mm. Hg, with four above 120; readings were not taken in the other six animals. The blood pressures were not increased in the rabbits given perfusates from adequately perfused placentas.

The blood pressure rises were probably secondary, since we have not been able to find pressor substances in acute experiments with placental perfusates.[5] Hypertension and vascular involvement are, of course, relatively late developments in pre-eclampsia as observed clinically.

Water Balance.—We have no quantitative data on the water balance, but in every rabbit injected with "ischemic" perfusates there was obvious water retention as shown by one or more of the following: oliguria, weight gain, edema, ascites, and occasionally hydrothorax. Of the eight rabbits receiving perfusates from adequately perfused placentas, five had some ascites or edema.

The nonprotein nitrogen of the blood was determined in five of the rabbits injected with "ischemic" perfusates. In the two which died in convulsions, the levels were 92 and 127 mg. per 100 ml., while the levels were normal in the other three. One rabbit receiving perfusate from adequately perfused placental tissue had a nonprotein nitrogen of 72, and Rabbit 11—consistently an exception in this series—had a terminal level of 197 mg. The others were normal.

The markedly positive water balance, with oliguria which was seen in all of the rabbits injected with "ischemic" perfusates, very probably can be correlated with our previous finding that such perfusates have an antidiuretic activity while those from placentas perfused at a more rapid rate usually do not inhibit diuresis. The azotemia probably depended in some degree upon the oliguria, although renal damage was also present.

Table I summarizes all of the data presented above.

Gross Pathology.—

Ascites: There was a slight increase in the amount of abdominal fluid in one of the rabbits injected with control perfusion medium (see above). There was no increase in the other two rabbits given perfusion medium or in the two injected with anoxic perfusates. Of the eight rabbits given perfusates from adequately perfused placentas, three had no increase in abdominal fluid, two had slightly increased amounts, two moderate, and one had marked ascites. Of the twelve rabbits injected with "ischemic" perfusates, three had no ascites; one other rabbit received intraperitoneal injections, virtually all of which had been absorbed at the time the rabbit was killed, four hours after the last injection. In the other eight rabbits, the degree of ascites was moderate to marked (marked = 50 to 70 ml.).

The protein content of the ascitic fluid was high, ranging from 3.02 to 7.20 Gm. per 100 ml. The fluids always clotted when removed from the abdominal cavities.

In general, the ascites was more marked in rabbits injected with "ischemic" perfusates, and the protein content of the fluids was higher in these animals.

Lung edema: Grossly, lung edema was obvious in only three rabbits, two of which were injected with perfusates from adequately perfused placentas. The other rabbit received "ischemic" perfusate.

TABLE I. OBSERVATIONS IN RABBITS INJECTED WITH PLACENTAL PERFUSATES

NO.	TOTAL DOSE ML.	FINAL BLOOD PRESSURE MM. HG	TERMINAL PROTEINURIA GM./LITER	BLOOD NONPROTEIN NITROGEN MG./100	CONVULSIONS AND DEATH	ASCITES		LUNG EDEMA	SUBENDOCARDIAL HEMORRHAGE	MOTTLED LIVER	RENAL EDEMA
						DEGREE	PROTEIN GM./100				
Control Perfusion Medium.—											
1	460	80	trace	–	0	0	–	0	0	0	0
2	260	90	1.2	33	0	0	–	0	0	0	0
8	260	85	5.3	–	Yes	Slight	–	0	0	Yes	Yes
Anoxic Perfusion.—											
3	760	–	4.0	86	0	0	–	0	0	0	Yes
13	260	100	2.7	31	0	0	–	0	Yes	0	Yes
Adequate Perfusion.—											
4	400	–	9.7	63	0	Slight	–	0	0	0	Yes
6	260	–	2.8	72	Yes	Moderate	–	0	0	0	Yes
11	280	–	2.8	197	0	Marked	3.75	0	0	Yes	Yes
20	240	80	–	–	0	0	–	0	0	0	0
21	120	–	3.7	–	Yes	0	–	Yes	0	Yes	Yes
22	360	–	–	–	0	Moderate	3.02	0	0	0	0
24	200	85	3.5	41	0	0	–	0	0	0	0
25	260	120	13.5	–	Yes	Slight	–	Yes	0	Yes	Yes
"Ischemic" Perfusion.—											
5*	60	–	Anuric	–	Yes	0	–	0	Yes	Yes	Yes
5a*	60	–	Anuric	–	Yes	0	–	0	Yes	Yes	Yes
7*	120	120	3.1	95	Yes	Marked	4.26	0	Yes	Yes	Yes
10	240	160	4.7	–	0	Marked	3.69	0	0	Yes	Yes
12	260	130	2.6	42	0	Slight	–	0	0	0	0
14*	100	–	57.6	–	Yes	Marked	6.52	0	0	Yes	Yes
15†	380	125	9.5	–	0	?	–	0	Yes	Yes	Yes
16*	240	85	13.1	42	0	Marked	4.20	Yes	Yes	Yes	Yes
17	220	85	5.2	32	0	Moderate	3.86	0	0	0	Yes
18	100	–	13.8	127	Yes	Moderate	7.20	0	0	0	Yes
19	60	–	–	–	Yes	Moderate	–	0	Yes	Yes	Yes
23	220	–	–	–	0	0	–	0	0	0	0

*Animals which showed significant microscopic pathology in the liver.

†Perfusate injected intraperitoneally; same perfusate as used in Rabbit 14.

Subendocardial hemorrhages: Pin-point to pin-head sized hemorrhages in the subendocardium of the ventricular septa were seen in one rabbit given anoxic perfusate, and in six (one-half) of the rabbits given "ischemic" perfusates.

Hemorrhages in this area are not infrequently seen in human eclampsia.

Mottling of the liver: A three-color mottling of bright red, dark red, and yellow was seen in one rabbit given control perfusion medium, three rabbits given perfusates from adequately perfused placentas, and eight (67 per cent) of the rabbits injected with "ischemic" perfusates.

Renal edema: Swelling of the renal cortex was a common finding in all groups of rabbits, as Table I shows. It was somewhat more frequent in the animals given "ischemic" perfusates (83 per cent).

Incidental observations: We[4] previously have reported that the surviving placental cotyledons produce gonadotrophin while in the Lindbergh pump. The ovaries of the rabbits which survived several injections of placental perfusates were amazing to behold. They were lumpy and black with many confluent *Blutpunkte*. The uteri showed evidence of marked estrogenic stimulation, being intensely congested, enlarged, and elongated. This observation does not, of course, demonstrate the placental production of estrogens. The animals' ovaries were intact, and also, in most instances, the initial perfusate was used. Initial perfusion might merely wash out hormone not necessarily produced in the placenta. Our experiments with estrogen production are incomplete, and will be reported later.

Microscopic Pathology

The description and interpretation of the microscopic pathology will be equivocal. One of us (L. C. C.) is in far over his depth, and has no opinion. The other of us (N. M. A., pathologist) is convinced that eclamptic lesions have been produced. Since Dieckmann did not accept the pathology as eclamptic, we have had several pathologists look at the slides—with a whole spectrum of opinions. At the suggestion of Arthur T. Hertig, we have had Doctor Ephraim Woll review the slides; he has had a wide experience in animal pathology. His comments are given in Table II, which summarizes the pathologic reports for the livers and kidneys of the rabbits.

Liver.—In the rabbits given control perfusion medium and anoxic perfusates, the liver pathology was minimal except that one of the latter animals showed marked fatty changes. Four of the eight rabbits injected with perfusates from adequately perfused placentas showed focal necrosis, sometimes peripheral, sometimes within the lobule. Fatty degeneration was reported in three others, and the remaining rabbit has severe coccidiosis which vitiated the experiment.

Focal necrosis was reported in the livers of seven of the twelve rabbits given "ischemic" perfusates. In several cases, the necrosis was limited to, or most marked at, the periphery of the lobules; in others it cut across the lobules. One of the pathologists examining the slides had many sections made for the purpose of teaching eclamptic pathology (Rabbit 7). Dr. W. J. Dieckmann, who very kindly looked at some of our material, did not accept this as eclamptic pathology on the ground that fibrin thrombosis of the capillaries was not seen consistently. Also, hemorrhage has not been a usual concomitant of the necrosis, although it occasionally has been.

Dr. W. E. Studdiford, who also saw the slides, wrote "the material which you have produced by slow perfusion seems to have caused a large variety of (liver) lesions varying from marked congestion to areas of focal necrosis with hemorrhage. Some of the latter lesions bear a striking resemblance to those found in eclamptic liver."

TABLE II. MICROSCOPIC PATHOLOGY IN RABBITS INJECTED WITH PLACENTAL PERFUSATES

NO.	LIVER		KIDNEY	
	WOLL	ALTER	WOLL	ALTER
Control Perfusion Medium.—				
1	Normal	Normal	Normal	Normal
2	Normal	Normal	Normal	Normal
8	Very occasional areas of necrosis	Fatty degeneration	Normal	Glomeruli shrunken and anemic; adhesions between tuft and capsule. Tubular epithelium shows much edema and necrosis
Anoxic Perfusion.—				
3	Normal	Normal	Tubules distended by casts. Glomeruli equivocal	Marked transition and swelling of epithelium. Glomeruli show early lesions—edema, cellularity, hemorrhage
13	Much glycogen (?)	Marked fatty changes	Normal	Edema and necrosis of tubular epithelium. Glomeruli anemic, capillaries contracted; adhesions between tufts and capsules
Adequate Perfusion.—				
4	Central focal necrosis	No report	Normal	No report
6	Severe acute focal necrosis	Occasional peripheral necrosis	Equivocal	Glomeruli anemic. Edema, necrosis, and hemorrhage in tubules
11	Extensive early necrosis	Early necrosis, peripheral and within the lobules	Tubules markedly distended by granular casts. Occasional glomerular capillary thrombosis and necrosis	Red cell casts. Glomeruli anemic, some necrosis; adhesions between tuft and capsule
20	No report	Marked fatty degeneration	Definite narrowing of glomerular capillary loops	Glomerular capillaries congested, edematous; adhesions between tuft and capsule. Marked destruction of tubular epithelium
21	No report	Peripheral thrombosis; necrosis in this area	No report	Glomeruli anemic, cellular and edematous; adhesions between tuft and capsule. Epithelium swollen; interstitial hemorrhages
22	No report	Fatty degeneration with hemorrhages	No report	Glomerular tufts swollen, anemic, adherent to capsules. Tubular epithelium swollen and vacuolized
24	No report	Severe coccidiosis	No report	No report
25	No report	Fatty degeneration	No report	Glomerular capillaries contracted; adhesions between tuft and capsule. Tubular epithelium swollen. Hemorrhages in capsule and interstitium

"Ischemic" Perfusion.—				
5	Focal necrosis	Focal necrosis, all at periphery (eclamptic type)	Possible slight narrowing of the glomerular capillaries	Practically no normal glomeruli—shrunken, anemic, adherent to capsules. Hemorrhages from afferent vessels
5a	Focal necrosis	Focal necrosis, all at periphery (eclamptic type)	Possible slight narrowing of the glomerular capillaries	Practically no normal glomeruli—shrunken, anemic, adherent to capsules. Hemorrhages from afferent vessels.
7	Severe acute focal necrosis	Very extensive necrosis around lobules and centrally	Many tubules filled with homogeneous material	All glomeruli shrunken and anemic; adhesions between tuft and capsule. Edema of stroma and tubules, with hemorrhage into collecting ducts
10	Kupffer cells prominent	Increased in endothelial cells	Questionable abnormality of the glomeruli	All glomeruli avascular; some show adhesions between tuft and capsule, some quite shrunken. Vacuolization of tubular epithelium
12	Large Kupffer cells	Increase in inflammatory cells at periphery	Glomerular epithelium swollen; capillary loops somewhat narrowed	Glomeruli anemic, capillaries contracted; adhesions between tuft and capsule. Hemorrhages in and between tubules
14	"Best example of severe focal necrosis"	Very extensive necrosis with hemorrhagic centers	Glomeruli ischemic with occasional necrosis; loops much narrowed	Glomeruli rather swollen. Edema of tufts and tubular epithelium. Hemorrhage into collecting tubules
15	Essentially normal	Small areas of hemorrhage at the periphery	Glomeruli more dilated than usual	Tufts anemic, capillaries contracted; adhesions between tuft and capsule. Free red cells in capsule. Tubular edema. Interstitial hemorrhage.
16	Central focal necrosis	"Indistinguishable from so-called textbook picture of typical human eclampsia"	No report	Glomeruli edematous, adherent to capsules; tufts anemic and shrunken. Hemorrhage into collecting tubules and between convoluted tubules
17	Very rich in glycogen	Fatty degeneration	Capillary loops narrowed. Casts in tubules	Glomeruli anemic; capillaries contracted; some show considerable edema and adhesions to capsules. Tubules edematous. Hemorrhages in capsules
18	Very early handsome focal necrosis	Hemorrhage and mild fatty degeneration and cloudy swelling	Glomerular capillaries narrowed	Glomeruli cellular, anemic, swollen. Capillary loops contracted. Marked edema of tubular epithelium. Interstitial hemorrhage
19	Very early handsome focal necrosis	Fatty degeneration with some areas of necrosis	No report	Glomeruli anemic; adhesions between tuft and capsule. Tubular epithelium edematous and granular
23	No report	Hemorrhages in the periportal spaces	No report	Glomeruli shrunken; no glomerular capillaries can be made out. Tubular epithelium swollen

In general, the "ischemic" perfusates were more likely to produce focal necrosis in the liver than were the other perfusates. As with the other pathologic findings, smaller doses of "ischemic" perfusates were effective—in fact, if the rabbit survived three or four injections of any of the perfusates (nine to thirteen hours after the first injection), the pathology usually was not impressive. Three of the rabbits died within ten hours of the first injection, and two of these (Nos. 5 and 5a) had quite marked areas of focal necrosis.

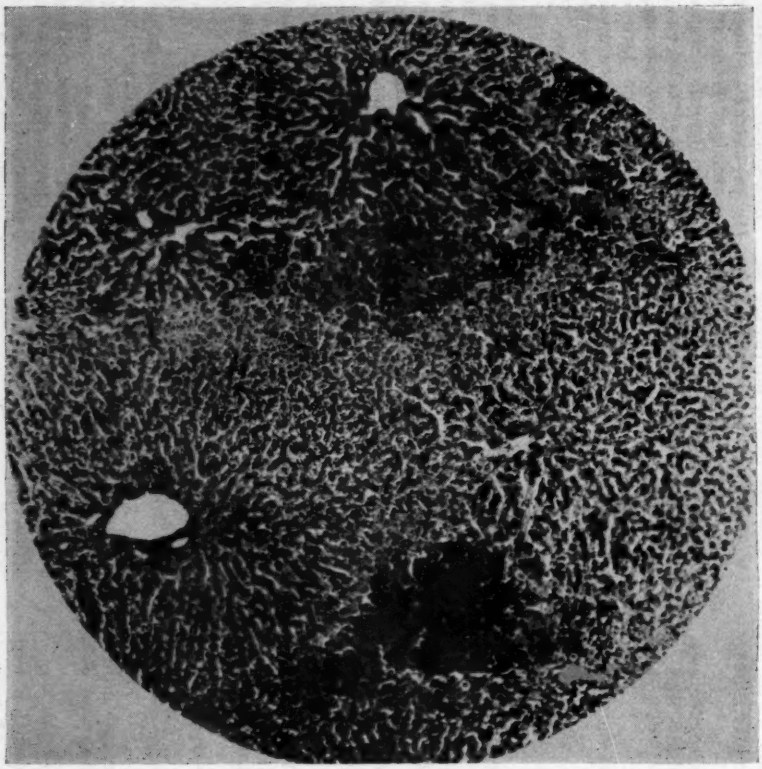

Fig. 1.—The liver of Rabbit 7. This area is typical for the livers of Rabbits 5, 5a, 7, and 16; nearly all fields show the lesion, focal peripheral necrosis.

Dr. Woll's comment is, "The lesions in the liver are very definite, and apparently represent several stages in development. Although coccidiosis was present in some of the animals, it was not related to the necroses. I have not seen such necroses in the animals which I have examined in this laboratory."

Kidney.—As Table II shows, pathologists can diverge. Dr. Alter considered that nearly every animal injected with placental perfusate had acute glomerulitis. His reports show somewhat more severe damage in the rabbits injected with "ischemic" perfusates. Dr. Woll reported normal glomeruli in the animals injected with control perfusion medium, anoxic perfusates, and all but two of the rabbits given perfusates from adequately perfused placentas. In the rabbits receiving "ischemic" perfusates, narrowing of the glomerular capillaries was a common finding (Woll). He wrote, "In no case was there thickening of the basement membrane of the glomeruli, or of the walls of the capillaries. On the other hand, there were many examples of narrowing of the capillary loops and, in a few instances, actual necrosis of the glomeruli."

The rabbits given "ischemic" perfusates showed more marked renal changes than the others, which probably correlates with their greater proteinuria, and possibly with their oliguria.

Other Organs.—The only brains examined were those of Rabbits 18, 24, and 25; they were edematous and congested. There was evidence of edema, with free fluid and thickening of the alveolar septa in many of the lung sections. The adrenal gland typically showed depletion, and occasionally hemorrhage as well. The ventricular septum of the heart showed such degenerative changes as edema, fragmentation of the fibers, hemorrhage, and hyalinization.

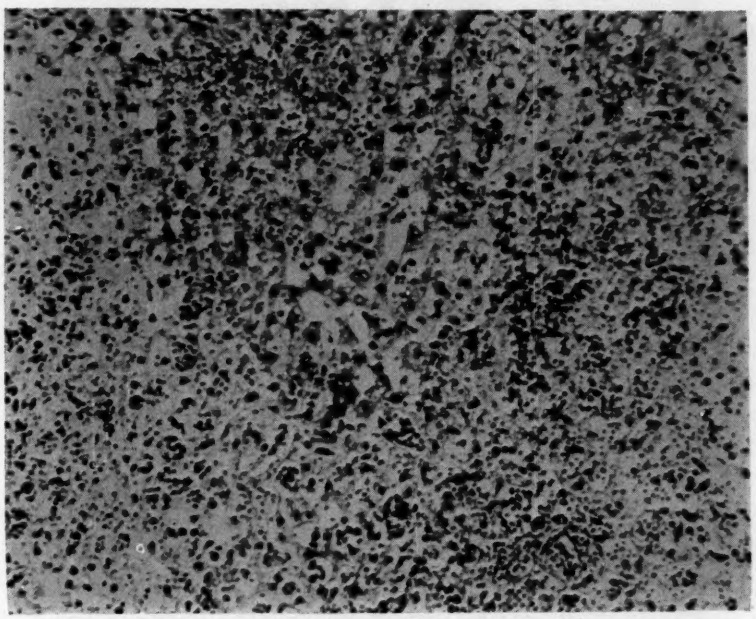

Fig. 2.—The liver of Rabbit 14, showing "acute yellow atrophy" type of lesion. This was found only in this rabbit, and in one dog.

Results in Dogs

Dog 1, a 10-week-old puppy, was given 580 ml. of "ischemic" perfusate subcutaneously. The others were given intravenous injections, using plastic tubing which was tied in the femoral vein. Since the dogs pulled out the tubing when left to their own devices, they were kept groggy or asleep with intravenous sodium pentobarbital. Dog 3 was infected, and Dog 9 apparently died from the anesthetic; these dogs will be excluded from the presentation of results. Dogs 2 and 4 were given perfusates from adequately perfused placentas; all others (Nos. 5 through 12) were injected with "ischemic" perfusates. The total dosages ranged from 500 to 1,300 ml.; the perfusates often had been kept in the refrigerator for periods up to five weeks, because they had to be accumulated before starting an experiment. Dogs 5 and 12 died after a period of coma; the others were killed by air embolism.

Proteinuria.—All but Dog 11 developed proteinuria. In Dogs 1 and 6 there was only a trace of proteinuria, while in the others it ranged from 1 to 5.6 Gm. per liter. Associated with the proteinuria were granular casts and many red blood cells.

Blood Chemistry.—The terminal blood nonprotein nitrogen was normal (21 to 33 mg. per 100 ml.) in all but Dog 12, in which it was 64 mg. per 100 ml. The carbon dioxide combining power was definitely decreased in every dog but one (No. 8), where it was 54 volumes. The icterus index was increased slightly (8.8 to 13 units). In Dog 12 the thymol turbidity was 4.1, in all others it was less than one unit.

Autopsy Findings.—The legs and abdominal walls were usually edematous. Gross ascites was not seen, but there was an excess of abdominal fluid in Dogs 2, 8, 11, and 12. This fluid clotted, and contained from 1.66 to 4.07 Gm. of protein per 100 ml. Lung edema was grossly recognizable in six (Nos. 4, 5, 8, 10, 11, and 12). In Dog 8 there were also hemorrhagic areas on the lung surfaces.

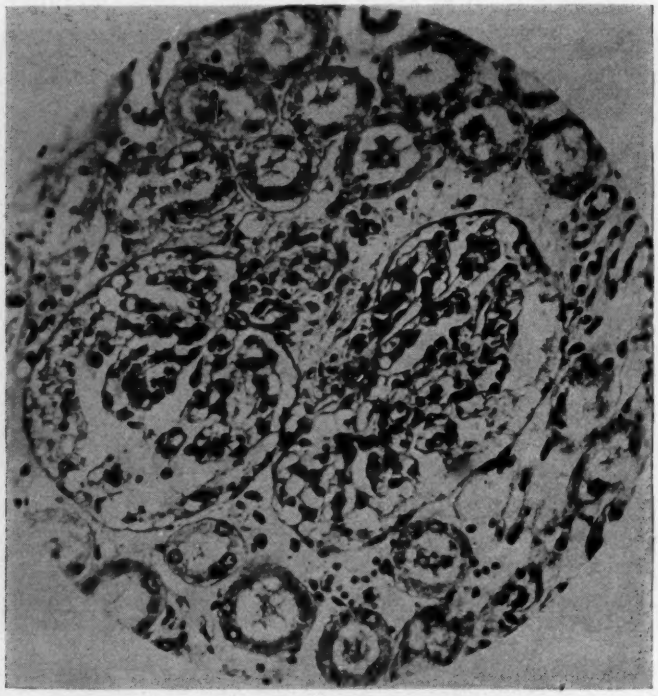

Fig. 3.—Kidney of Rabbit 5, showing glomerulitis, interstitial edema, and early necrosis of the proximal convoluted tubule. These lesions were frequent (see Table II).

Only Dog 12 showed macroscopic hemorrhages of the ventricular septum; this heart also had hemorrhages over the surface. The liver was mottled (three-color) in six (Nos. 6, 7, 8, 10, 11, and 12); the liver constituted from 4.63 to 5.02 per cent of the initial body weight in all dogs except No. 12, where it was only 2.54 per cent. The kidneys were swollen in every instance, the cortical edema being conspicuous. In Dog 5 there was a striking concentric banding in the renal cross section, with a middle band of dark red at the corticomedullary junction, flanked by pale bands. The brain was edematous and congested in Dogs 7, 8, 10, 11, and 12; the brain of Dog 4 was grossly normal, but microscopically showed pin-point hemorrhages in the basal ganglia. In Dog 12 there was subdural hemorrhage, and cross section showed scores of punctate hemorrhages. The other brains were not examined.

Microscopic Pathology.—Dr. Alter diagnosed acute glomerulitis in every dog, Dr. Woll in none. They agreed that the glomeruli were often anemic, and that renal degeneration was impressive in Dogs 7 and 12. The tubular epithelium was edematous and sometimes necrotic, and there were hemorrhages in the interstitial spaces and between the tubules, in some cases.

The outstanding change in the liver was a tremendous engorgement of the capillaries, with swelling and vacuolization of the liver cells (pressure atrophy?). Focal necroses (chiefly central) were seen in the livers of Dogs 1 (peripheral only), 5, 7, and 8. Dr. Alter described hemorrhages in the livers of Dogs 2, 5, 6, 7, 10, 11, and 12. Dr. Woll saw only marked congestion.

One of the most consistent findings was acute myocardial degeneration. Sections of the ventricular septa showed edema, fragmentation, and usually hemorrhage in Dogs 5, 6, 7, 8, 10, 11, and 12. The adrenals were depleted in Dogs 4, 6, 10, and 12; in Dogs 10 and 12 they were hemorrhagic as well.

The brain of Dog 4 had pin-pint hemorrhages in the basal ganglia; that of Dog 12 had many punctate hemorrhages in the cerebrum, cerebellum, and basal ganglia.

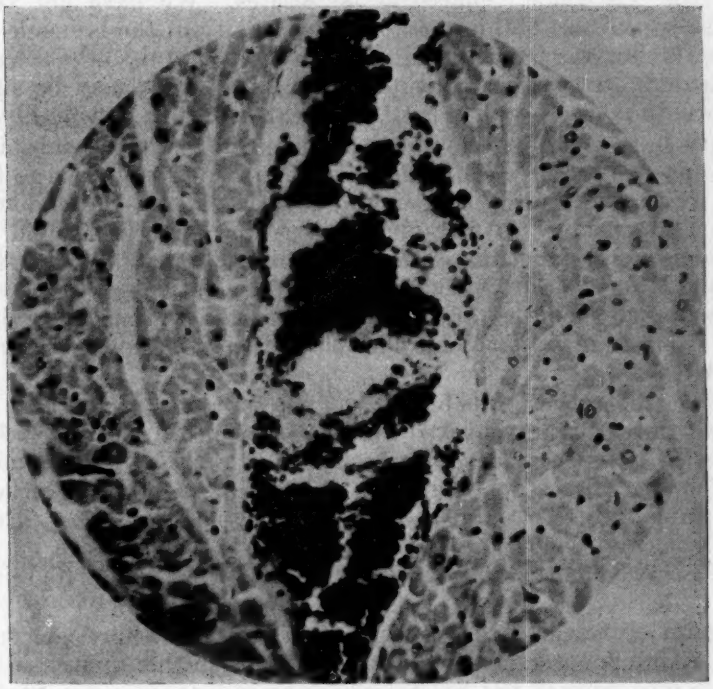

Fig. 4.—Heart muscle of Dog 11, showing hemorrhage. This was a frequent lesion in both the rabbits and the dogs.

In summary, the most pronounced abnormalities were found in Dogs 5, 6, 7, 8, 10, 11, and 12—the dogs given "ischemic" perfusates. Dog 12, which died after two days of coma, received 900 ml. of "ischemic" perfusate. The proteinuria in this dog was not impressive—1.4 Gm. per liter. The blood chemistry was the most abnormal seen. The abdominal and chest cavities contained a moderate amount of fluid with a protein content of about 4 Gm. per 100 ml. The lungs were grossly edematous, with areas of hemorrhage. There were hemorrhages over the surface of the heart and in the subendocardium. The liver was shrunken, mottled with three colors, and the tips of the lobes were hemorrhagic. The kidneys were markedly swollen, and there were hemorrhagic areas throughout the cortices. The brain was edematous, and showed scores of punctate hemorrhages on cross section; also, there was subdural hemorrhage. Microscopically, the liver showed "marked congestion and hemorrhage throughout" (Dr. Alter), intense congestion with minimal atrophy" (Dr. Woll). The kidneys: "There is congestion and a great deal of hemorrhage between the tubules. Tubular epithelium is markedly swollen; there is necrosis and loss of nuclei. Glomeruli are cellular and anemic, but hemorrhage is seen between tuft and glomeruli where there is also a great deal of edematous fluid" (Dr. Alter). "Very impressive degeneration; thrombi, precipitated hyaline bodies" (Dr. Woll). The adrenals were intensely depleted and hemorrhagic.

Discussion

We have not used pregnant animals, or even females exclusively, in this series of experiments, because we thought that if the ischemic placenta did produce a toxin its effect should be manifested in any animal injected with it. A pregnant animal might be more, or less, sensitive, and we mean to follow up this phase of the work.

The results described do indicate the presence of a toxic substance, or substances, in the "ischemic" placental perfusates. We have not yet perfused other organs, so can say nothing as to the specificity of the ischemic placenta as a source for this toxin. One might expect any ischemic tissue to release proteins and protein derivatives of varying toxicities. Our work may be significant in that the placenta is in a peculiar position of exposure to a deficient blood supply.

We have not attempted to isolate or identify the toxic substance, partly because its appearance has been rather erratic. It does not seem to be the toxic euglobulin which the Smiths have found to originate in the endometrium because: (1) our substance is filtrable through Seitz and Berkefeld filters, and (2) it is much more stable than the Smith's euglobulin. The perfusate which killed Rabbits 5 and 5a within ten hours (three injections) was kept at summer temperature for two months, and then given to Rabbit 7. This rabbit died in convulsion after six injections, and had marked liver pathology of the eclamptic type (Dr. Alter).

The toxic substance probably is not thromboplastin, because: (1) it is filtrable; the only filtrate checked for thromboplastic activity was negative. Thromboplastin is not considered to be filtrable. (2) Fibrin thrombi were not often found in the microscopic sections. (3) The animals were not defibrinated; the ascitic fluids clotted, as did the postmortem blood samples. Furthermore, such large molecules as those of euglobulin and thromboplastin may well have been excluded from entry into the perfusates, which circulated in the fetal vessels.

It is quite conceivable that several toxic substances are concerned in the production of human eclampsia. Page's hypothesis that placental (or gravid uterine) ischemia leads to the release of a toxic substance, or substances, is still a hypothesis. However, it strikes us as being a very reasonable one, which pieces together many of the facts which have been established as to the incidence of toxemia. As was just mentioned, such ischemia might be expected to result in the release of many proteins and protein derivatives.

Thromboplastin may be one of the "toxins," and its release from the placenta (one of the richest sources in the body) could well account for the fibrin thrombosis seen in many sites, in human eclampsia. In this connection, Dieckmann[6] produced "eclamptic pathology" in the dog's liver by the injection of "tissue fibrinogen" (probably thromboplastin) into the portal circulation. Thromboplastin would also account for the increased coagulability of the blood, often seen in pre-eclampsia, and the later loss of coagulability occasionally seen in severe, defibrinated cases of toxemia.

Fibrin thrombosis and alterations in the blood coagulability are relatively late changes in toxemia of pregnancy; we must still explain the early alterations, of which water and salt retention are perhaps the most important.

We have reported previously that "ischemic" placental perfusates contain an antidiuretic substance; the marked water retention seen in the animals described here is probably attributable to this factor. Ham and Landis[8] found a similar—or the same ?—antidiuretic substance in extracts of placentas from patients with pre-eclampsia, but not in placentas of normal parturients. This antidiuretic factor may be another of the "toxins" concerned in pre-eclampsia;

certainly water retention is an early sign of developing pre-eclampsia, and the mechanism of the positive water balance has never been elucidated.

Perhaps a third "toxin" related to pre-eclampsia is the substance, other than the antidiuretic factor, with which we have been working. Simple salt and water retention alone does not explain the pathology of eclampsia, or the pathology seen in our animals. It may be, too, that our toxic substance bears no relation to pre-eclampsia—we do not know.

Summary

Cotyledons of human placentas have been perfused aseptically in Lindbergh pumps. The perfusates have been filtered through Seitz or Berkefeld filters, and injected intravenously into rabbits and dogs at four-hour intervals.

When the placental cotyledons were perfused very slowly (artificial placental ischemia), the perfusate was often toxic.

Toxic manifestations included blood pressure rises (in rabbits), proteinuria, oliguria, edema, convulsions (in rabbits), and death.

Autopsy findings in these animals included ascites, mottling of the liver, renal edema, hemorrhages in various sites, especially the subendocardium and brain, and lung edema.

Microscopic pathology, especially in the rabbits, included focal necroses in the liver sometimes associated with hemorrhage, acute myocardial degeneration, lung edema, adrenal depletion, renal tubular degeneration, and narrowing of the glomerular capillaries.

These experiments reproduce some of the features of human eclampsia, but pathologists are divided on the question as to whether the microscopic pathology is that of eclampsia.

We wish to acknowledge our very great indebtedness to Dr. Herbert S. Gasser, Mr. Edric B. Smith, and Mr. John Campo, of the Rockefeller Institute, for the loan of the Lindbergh pumps. Dr. Irene E. McFaul initiated us in the techniques of organ culture. Mrs. Doris Monroe and Mrs. Eleanor Chesley assisted in setting up the perfusions. Mrs. Elizabeth Chesley helped with the animal experiments. We are especially grateful to Dr. Ephraim Woll, of the University of Vermont College of Medicine, for a painstaking review of the microscopic pathology. Also we wish to thank Drs. William J. Dieckmann, William E. Studdiford, and many others for examining the slides.

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VAGINAL DELIVERY FOLLOWING CESAREAN SECTION*

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VAGINAL delivery, if less hazardous, can be substituted in cases meeting certain requirements. With this in mind, our cases have been reviewed to determine whether the risk of pelvic delivery is less than that of repeat cesarean section. With the conservative management of abruptio placentae, placenta previa, the toxemias, and the evaluation of dystocias by careful clinical and x-ray mensuration, cesarean section now comprises approximately 5 per cent of deliveries at most leading clinics.

However, despite careful discrimination in the selection of indications for cesarean section, adherence to the dictum "once a cesarean section, always a cesarean section" will once again, with a number of repeat sections, push this procedure into the unacceptable percentage brackets. We hold, with Waters, Stander, Phaneuf, Cosgrove, Hindman, and others, that repeat cesarean sections are not invariably necessary.

Much of the decision as to the management of a previously sectioned patient rests on the evaluation of the uterine scar. Experimental investigations and studies of excised scars and excised uteri containing such scars have shown that healing is effected by fibroblastic proliferation. According to Schwarz, Paddock, and Bostnick, ". . . the healing process takes place chiefly by proliferation of fibroblasts along the line of incision entering the spaces between the adjacent muscle bundles. As the scar shrinks, this becomes less perceptible and it is difficult to demonstrate the line of incision with ordinary hematoxylin-eosin stain after a two weeks' period. Special stains, namely Van Gieson, bring out this differentiation.

". . . In uteri removed after previous cesarean section the scar is frequently imperceptible, but in many instances increased connective tissue can be demonstrated. The reason that the scar is imperceptible is due to the marked shrinkage of the newly developed connective tissue and the fact that it branches off in between the muscle bundles along the line of incision. If the suturing has been done well, the muscle edges are in close apposition, which necessitates only a narrow line of healing. As this shrinkage takes place, the normal relationship of smooth muscle and connective tissue, as occurs in normal pattern of the non-injured uterus, is similar."

The strength of such well-healed scars is even greater than of the muscle itself. This has been evidenced both clinically and experimentally. Mason and Williams in 1910 took uterine muscle strips containing cesarean section scars (guinea pigs and cats) and subjected them to progressive stretching by means of increasing weights. The site of resulting rupture was always in the

*Presented, by invitation, before the Obstetrical Society of Boston, Nov. 21, 1950.

muscle and not in the scar. Clinical reports of rupture through the muscular portion of the gravid uterus, while the scar remains intact, indicate the relative strength of the two tissues.

Defective scars, however, are weak. From the ideal, firmly united, strong scar described above, there are all gradations to a scar consisting only of peritoneum and decidua. The principal causes of weak scar are infection and faulty surgical technique. Perfect coaptation may be prevented by leucocytic infiltration associated with tissue necrosis—the ultimate result, a wide weak scar. Technical errors, such as improper apposition of tissues, excessively tight suturing, faulty knots, et cetera, all contribute to defective scar formation. Cooke, in discussing wound healing, pointed out that tissue necrosis resulting from excessively tight knots was probably a greater factor in the production of a weak scar than was infection or the failure to close in layers.

Presumed causes of weak scar, such as the location of the uterine incision and the character of the suture material, are disputed. English writers seem to prefer classical section. American obstetricians generally favor the low segment approach. Furthermore, Waters and Phaneuf believe that a transverse, low cervical incision is safer than a vertical one. Despite these various preferences, the critical observation of Falls, Schuman, and others revealed only little difference in the result of the two types of cesarean section when comparable cases were analyzed.

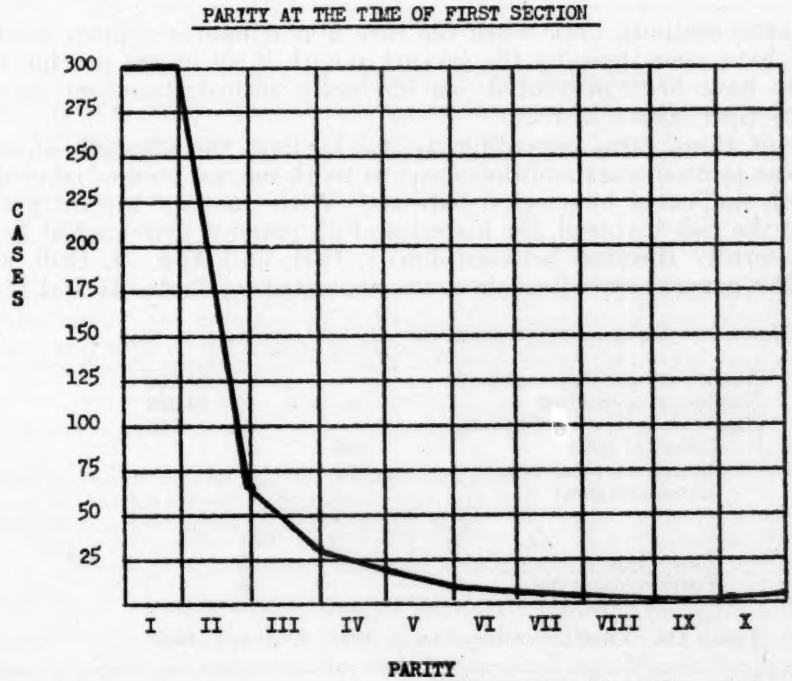

Fig. 1.

Regarding suture material, opinions are also divided. Price, Kennedy, Babcock, and Potter advocate the use of nonabsorbable, nonirritating suture materials, but the excellent results obtained by the use of the catgut technique indicates that wound healing is less dependent on the material than on the method. Supporting this latter view is the work of Bowers, Burns, and Mengle with fine 5-0 chromic catgut suture in surgery of the gastroenteric tract, the biliary tract, and in the suturing of dura, tendon, nerve, and fascia.

Other factors advanced as predisposing or contributing to weak scar formation are the influence of placental implantation over the scar and the effect of overdistention on the scar. In a well-healed scar, neither factor affects the scar in any way. In a defective scar, however, chorionic invasion may occur and accentuate the weakness of the scar or overdistention may result in disruption of the scar.

The argument that a routine repeat section should be done as a prophylaxis against uterine rupture is not absolutely valid. A review of the literature will reveal many instances of rupture occurring before term. Swift reported a case of spontaneous rupture at three months' gestation following a classical section and an abdominal pregnancy. LaMariana, in 1932, found twenty-four cases in which rupture occurred before term; seven ruptured in the seventh month of pregnancy.

TABLE I. TIME OF UTERINE RUPTURE. REVIEW OF LITERATURE BY PETER LAMARIANA (1932)

Full term	110
Eight months	12
Seven months	7
Eight and one-half months	5
Eleven months	1
Total	135

Prophylactic sections, even when the rare first trimester rupture is eliminated, must have been done by the seventh month if all of the uterine ruptures were to have been prevented—an obviously absurd statement, as was pointed out by Karl Wilson in 1926.

In view of these facts regarding wound healing, the strength of well-healed cesarean section scars and the causes of weak scars, a trial of labor does not seem contraindicated in selected patients. With the view toward proper evaluation of the risk involved, the histories of all patients delivered at Lewis Memorial Maternity Hospital between Jan. 1, 1931, and Aug. 31, 1950, were reviewed. The general statistical data are presented in Tables II and III.

TABLE II. GENERAL STATISTICS, JAN. 1, 1931, TO AUG. 1, 1950

Number of patients registered			28,259
Number of deliveries			36,293
Number of cesarean sections			585
Classical type	300		
Lower cervical type	269		
Extraperitoneal	3		
		572	
Porro type		7	
Posthumous type		6	

TABLE III. COMPLICATIONS, JAN. 1, 1931, TO AUG. 1, 1950

Total number of ruptured uteri		10
With section history	6	
Without section history	4	
Abdominal pregnancy		1
Pubiotomies		5
Craniotomy		1
Maternal deaths		57
Following section	12	
Without section	45	

The total number of patients with histories of cesarean section (or sections), whether performed at Lewis Memorial Maternity Hospital or else-

where, was 448. Of these 448, 128 were subjected to one or more repeat sections and 62 were successfully delivered via the vaginal route.

TABLE IV. NUMBER OF SECTIONED PATIENTS (POSTHUMOUS SECTIONS NOT INCLUDED)

Total number with history of cesarean section		448
1 section (including Porro in 4)	320 (71.4%)	
2 sections (including Porro in 3)	87 (19.4%)	
3 sections	31 (6.9%)	
4 sections	8 (1.8%)	
5 sections	2 (0.4%)	
Total number delivering vaginally after a section		62
or 13.9% of all patients with section		
or 32.6% of all patients with *previous* section		

Thus 32.6% of the 190 patients with a history of section at the preceding pregnancy were so delivered. Of the 62 patients, 56 were delivered of their first pregnancy following the cesarean section at Lewis Memorial Maternity Hospital.

TABLE V. PLACE OF SECTION AND VAGINAL DELIVERY

Section elsewhere, first vaginal delivery elsewhere	6
Section elsewhere, first vaginal delivery at L.M.M.H.	21
Section and first vaginal delivery at L.M.M.H.	35
Total	62

TABLE VI. PARITY AT TIME OF SECTION

	I	II	III	IV	V
Section elsewhere, first vaginal delivery elsewhere	5	1	0	0	0
Section elsewhere, first vaginal delivery at L.M.M.H.	18	0	2	1	0
Section and first vaginal delivery at L.M.M.H.	18	10	4	1	2
Total	41	11	6	2	2

There were 106 deliveries in the 62 patients. In Table VII is shown the distribution of the number of deliveries subsequent to the section; while the number and type of deliveries are shown in Table VIII.

TABLE VII. NUMBER OF DELIVERIES FOLLOWING SECTION

	I	II	III	IV	V	TOTAL
Section elsewhere, first vaginal delivery elsewhere	0	2	2	1	1	6
Section elsewhere, first vaginal delivery at L.M.M.H.	15	2	3	1	0	21
Section and first vaginal delivery at L.M.M.H.	20	11	2	2	0	35
Total	35	15	7	4	1	62

TABLE VIII. TYPES OF DELIVERY FOLLOWING SECTION

	I	II	III	IV	V	TOTAL
Spontaneous	34	19	9	5	1	68
Forceps:						
Not specified	2	2	–	–	–	4
Outlet	1	1	1	–	–	3
Low	20	–	–	–	–	20
Mid	2	–	–	–	–	2
Breech extraction	2	2	–	–	–	4
Version and extraction	1	1	–	–	–	2
Pubiotomy	–	–	1	–	–	1
Subsequent section	–	1	1	–	–	2
Total	62	26	12	5	1	106
Twins	3	1	1	–	5	

Since six of the 62 patients had both the cesarean section and the first subsequent vaginal delivery elsewhere, only a remaining 56 had a "trial of labor" which could be evaluated. Of these 56 patients, 35 had had the operation at the time of the first pregnancy (therefore they were primiparas, and to be referred to as a primipara section group), and 21, after the first parity (therefore, they were multiparas, and to be referred to as a multipara

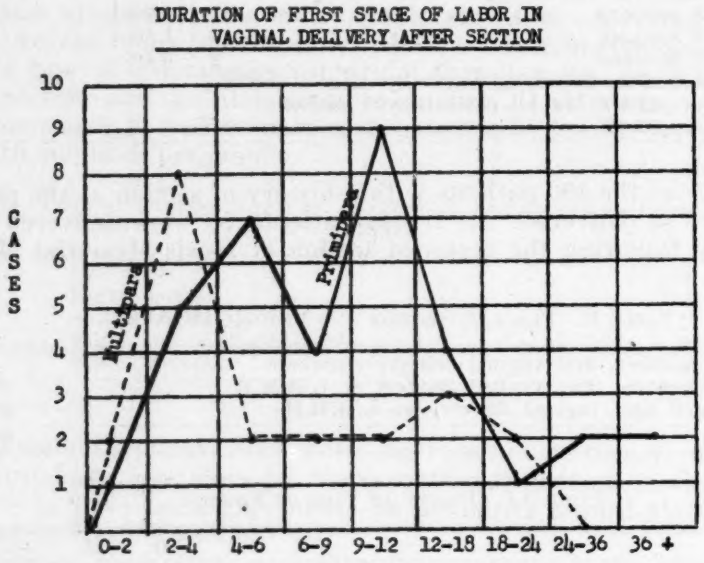

Fig. 2.

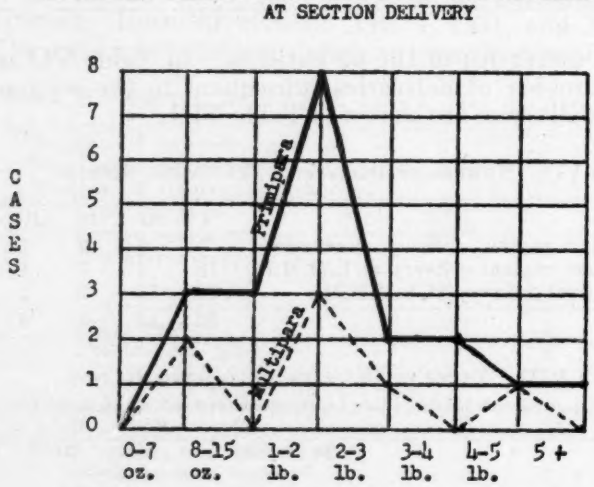

Fig. 3.

section group). The duration of labor for the first vaginal delivery following a section for the two types of patients is shown in Fig. 2. Comparative birth weight studies (Fig. 3) revealed that 20 primiparous sectioned and seven multiparous sectioned patients were delivered of larger infants at the subsequent delivery than at the section delivery. This is important from two stand-

points; first, that the clinical impression of disproportion may be erroneous; and second, that overdistention per se does not cause a weak scar, as has been previously discussed. Reference to Table IX shows eleven patients sectioned for disproportion. Six of such patients had larger infants at the subsequent vaginal deliveries, and two additional patients had twins with their first pregnancy following section.

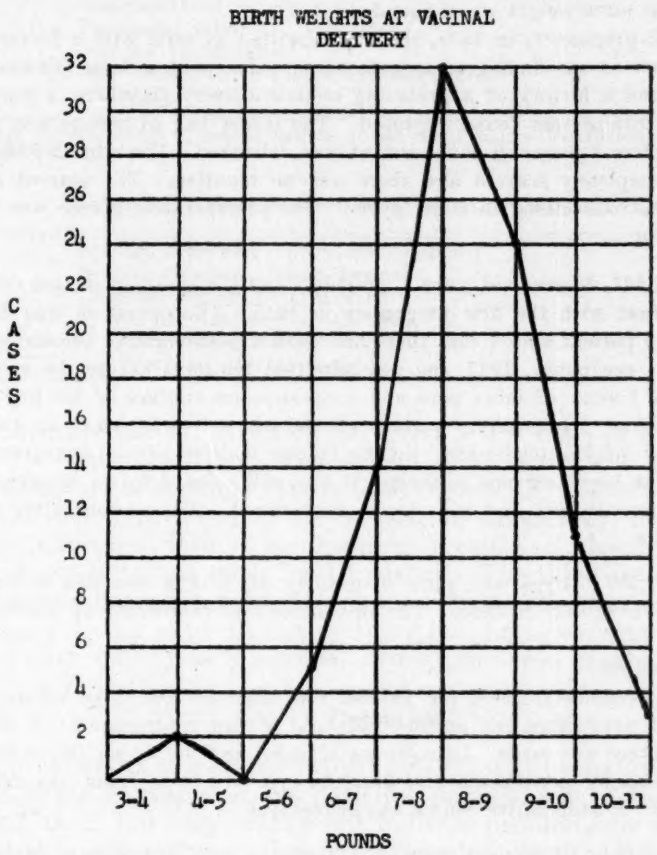

Fig. 4.

The type of cesarean section preceding the vaginal delivery is shown in Table X. Since 1942, the low cervical section has been employed almost exclusively and the transverse incision generally favored over the vertical one. The number of successful vaginal deliveries following the classical section, however, seems to indicate that the site of incision does not contraindicate a "trial of labor." There have been, however, six instances of uterine rupture in patients with a history of section. Because of their importance, the six cases are abstracted here:

CASE 1.—No. 8161, 40-year-old, para i, gravida ii. Her first pregnancy in 1934 was terminated at the thirtieth week by a classical section for "eclampsia." The fetal weight was 3 pounds, 13 ounces. Closure was in 4 layers. Postoperative course was uneventful and afebrile.

With her second pregnancy, in 1936, she was admitted thirteen days prior to the expected date of confinement in a state of shock. The accompanying relatives stated that the patient suffered sudden onset of pain which rapidly became continuous in nature. She was

treated for shock. After two days, she was operated upon and found to have a ruptured uterus with complete extrusion of the intact placenta and bag of waters into the peritoneal cavity. The infant was dead. The uterus was well contracted but was removed subtotally. The convalescence was uneventful and afebrile.

CASE 2.—No. 15,521, 23-year-old, para i, gravida ii. Her first pregnancy occurred in 1937, and she was delivered by cesarean section at an outside hospital. The indication was not given, but the fetal birth weight was 9 pounds.

With her second pregnancy, in 1939, she was admitted at term with a history of onset of mild labor. In view of our finding of a justo minor pelvis with a false promontory being reached at 11.0 cm. and a history of a preceding section delivery elsewhere, a repeat section was performed. The uterus was found ruptured. The intact bag of waters was protruding through the rent. A live 7 pound, 6 ounce infant was delivered. The edges of the ruptured wound were found completely scarred and there was no bleeding. The scarred edges were excised, and the uterus was closed in four layers. The postoperative course was completely afebrile and uneventful.

CASE 3.—No. 22,537, 32-year-old, para i, gravida ii, with a cesarean section delivery of a 9 pound stillborn infant with the first pregnancy in 1945. The operation was done at another hospital, but the patient stated that there had been a postoperative hemorrhage.

With her second pregnancy, 1947, she was admitted ten days before the expected date of confinement with a history of labor pain and a spontaneous rupture of the bag of waters. Preoperative diagnosis of "impending rupture of the uterus" was made on the basis of strong labor pains and marked tenderness over the former incision site. Laparotomy revealed an early rupture of the lower segment, although it was still covered by an intact peritoneum. A live term fetus was delivered and the uterine rent closed. The postoperative course was uneventful and afebrile.

CASE 4.—No. 22,537, 34-year-old, para ii, gravida iii, with a cesarean section delivery of a 9 pound stillborn infant in 1945. The operation was performed at another hospital for central placenta previa. A repeat cesarean section was performed at Lewis Memorial Maternity Hospital in 1947.

With the third pregnancy, 1948, the patient was admitted ten days before term with a history of ruptured membranes and an onset of mild uterine contractions. A diagnosis of impending uterine rupture was made. Laparotomy revealed an 8 by 12 cm. defect in the lower uterine segment covered by peritoneum and placenta. A live term fetus was delivered via cesarean hysterectomy. Postoperative course was uneventful.

CASE 5.—No. 25,771, 18-year-old, para i, gravida ii, with a cesarean section delivery with the first pregnancy at another hospital. Indication outlet disproportion. Fetal weight 6 pounds, 8 ounces. The patient was hospitalized four weeks from term because of a sudden sharp pain in the vicinity of the bladder. Diagnosis of ruptured uterus was confirmed at laparotomy. A stillborn fetus and a placenta were found in the peritoneal cavity, and a 15 cm. rent noted in the upper uterine segment. The scarred edges of the rent were freshened and the uterus closed. Postoperative course was uneventful.

CASE 6.—No. 26,248, 31-year-old para iii, gravida iv, with a history of cesarean section at another hospital at the time of the third pregnancy. The indication was rising Rh titer. Elective repeat cesarean was performed at Lewis Memorial Maternity Hospital for placenta previa and an occult prolapse of the cord. An 8 by 9 cm. defect in the lower segment was found at laparotomy. A living infant was delivered by cesarean hysterectomy. The postoperative course was morbid due to breast engorgement.

Thus, in the six cases of ruptured uterus, there was no maternal mortality and one case of morbidity. The fetal salvage was 67 per cent.

The fetal outcome in the 106 successful vaginal deliveries was: 5 sets of twins, 3 fetal deaths, and one 3 pound, 3 ounce premature infant who survived. Of the three deaths, one infant was delivered vaginally because of the diag-

TABLE IX. INDICATIONS FOR THE SECTIONS

Placenta previa		16
Abruptio placentae		4
Toxemias of pregnancy		9
Eclampsia	2	
Pre-eclampsia	6	
"Toxemia"	1	
Toxemia and antepartum bleeding		1
Disproportion		11
Prolonged labor		4
"Weak indications"		4*
Not determinable (sectioned elsewhere)		13
Total		62

*Desire for live child 1, double vagina 1, old third degree laceration 1, compound presentation, prolapsed foot 1.

TABLE X. TYPES OF SECTION PRECEDING VAGINAL DELIVERY

Section elsewhere (probably classical)		24
Section elewhere, lower cervical		4
Classical section at L.M.M.H.		24
Lower cervical section at L.M.M.H.		10
Transverse uterine incision	7	
Vertical uterine incision	3	

nosis of intrauterine death which occurred a few days prior to the scheduled date for the repeat section. The second fetal death was that of a 5 pound, 2 ounce fetus with hydrops fetalis delivered eight weeks prematurely. This mother had been sectioned at the preceding pregnancy, her fifth, ten weeks before the expected date of confinement because of bleeding, only to have a 3 pound, 3 ounce infant with fetal hydrops. The third fatality occurred in a ten weeks premature 3 pound, 1½ ounce infant, who survived only ten hours. The section delivery prior to this delivery had been performed elsewhere. The weight of that fetus was 3 pounds. Thus, all these deaths were nonpreventable.

Comment

The proponents of routine repeat section will probably point out that an incidence of six ruptures in 190 patients, particularly of the silent kind illustrated by Case 2, not only justify but indicate prophylactic section. They will state that it is impossible to determine which patient is going to suffer a ruptured uterus. Cases of rupture occurring after an interval of vaginal deliveries are cited as evidence. Yet, the same worker will agree that an attempt at vaginal delivery is indicated when the fetus is dead. This seems inconsistent. The maternal risk in a ruptured uterus is the same regardless of the state of the fetus.

The mortality following a rupture of cesarean scar is estimated to be around 10 to 15 per cent. Burkons reported an incidence of 11 per cent and stated that the obstetrician who favors vaginal delivery following a section assumes less risk than if he routinely resectioned all patients. His logic was as follows: the average incidence of rupture following classical section is 4 per cent; of this 11 per cent may be expected to die—an incidence of 0.44 per cent of the original number; whereas, the basic mortality in the resection cases as reported by Skeel and Jordan, quoting Burkons, is 1 to 2 per cent. McLane found no uterine rupture and no maternal mortality in his series of 43 cases. Duckering, of Stander's clinic, reported eight cases of ruptured uteri in previously sectioned patients with no maternal mortality. She attributes this to the careful observation and prompt treatment. There was no mortality in our six cases of ruptured uteri.

There is little doubt that the maternal risk in a rupture through the old section scar is less than that resulting from ruptured uteri occurring in patients without such a scar. Burkons found shock present in only two of the eighteen rupture patients with section scar, while shock was the prominent condition in 23 of the 27 uterine ruptures in patients without a scar. It seems logical, therefore, that certain conditions should indicate a "trial of labor" as the management of choice in certain selected patients. This management, of course, must be under an experienced, well-qualified obstetrician at a hospital equipped to meet all emergencies. These conditions are:

1. Early engagement of the presenting parts. This condition facilitates evaluation of the cervical status, particularly during labor. In 14 of 56 patients, engagement occurred three to five weeks before the onset of labor.
2. History of vaginal deliveries preceding the section delivery. The comparatively lighter and shorter labor of each succeeding pregnancy indicates the relative ease of effacement and dilatation of the cervix. The greater the number of vaginal deliveries preceding the section, the easier and shorter may be the expected labor. Fig. 2 confirms this impression.
3. Diagnosis of death or monstrosity in utero. Uniformity of opinion is approached regarding this indication. In one of our patients scheduled to have a repeat section on the basis of previous section by an unknown operator, intrauterine fetal death was diagnosed five days prior to the date of the scheduled operation. She was, therefore, permitted to go into spontaneous labor and delivered a 7 pound, 11 ounce macerated stillborn infant after twelve hours of labor.
4. Reasonable assurance of a well-healed scar. As has been discussed, a well-healed, strong scar may be reasonably expected when surgical technique is known to be good and the postoperative course uneventful and afebrile (i.e. free of infection). This plus the absence of the original indication for the section will indicate a trial of labor.

The significance of successful vaginal delivery subsequent to a section delivery is obvious. Once a patient has had such a delivery, the contraindication to a careful "trial of labor" is almost completely removed. Even the most ardent advocate of repeat section will concede that an attempt is justified with all subsequent pregnancies (for that patient). This becomes of greatest importance when it is realized that the majority of the first sections are performed on primiparous patients (Fig. 1), how often operations are done on erroneous indications (Table IX), and the fact that some authorities attach so much danger to repeated sections that routine sterilization is practiced after the second or the third cesarean section! A successful vaginal delivery, then, at least partly corrects what Kennedy refers to as "tragedies of the uterine incision incident to the cesarean section."

The danger of uterine rupture occurring during labor is admitted. We have had six in our 190 patients. Furthermore, a successful vaginal delivery does not guarantee against a future rupture. Fava, Casagrand, and others have reported uterine ruptures occurring following cesarean section, but with normal deliveries in the interval between. Dieckmann mentions a case following an interval of two vaginal deliveries. On the other hand, Mason and Williams (1910) and Lemeland and Lacomme (1933) have reported cases with vaginal deliveries following three preceding sections. In general, the greater the number of vaginal deliveries, the less likelihood is there of rupture. The danger, however, is always present, so that every gravida with a history of cesarean section must be observed carefully at all times and particularly in the last trimester. All complaints of vague abdominal pain and tenderness

must be carefully evaluated so that when rupture does occur or can be anticipated, prompt appropriate measures may be taken. Under such a regime, the maternal risk may be kept at a minimum consistent with the justification for an attempt at vaginal delivery.

Summary

The literature has been reviewed regarding wound healing, the causes of weak scar, and the risks involved in ruptured uteri following cesarean section. There seems to be definite indication for an attempt at vaginal delivery under certain circumstances as outlined.

The twenty years' survey at the Lewis Memorial Maternity Hospital revealed that 62 (or 32.6 per cent) of the 190 patients with a history of cesarean section were successfully delivered via the vaginal route. The incidence of ruptured uteri was 6 (or 3.6 per cent) but not in the ones subjected to a trial of labor. There was no maternal mortality and only one case of morbidity due to breast engorgement. The fetal salvage was 67 per cent. In 41 out of 62 vaginal delivery patients, the cesarean section had been done at the time of primiparity; in the remaining 21, one to four vaginal deliveries preceded the section. The maximum and minimum duration of the first stage of labor in the first vaginal delivery following the section were 56 hours, 15 minutes, and 1 hour, 21 minutes, respectively, in patients sectioned as primiparas; and 23 hours, 9 minutes, and 2 hours, 35 minutes, respectively, for patients sectioned as multiparas. Twenty primiparous sectioned patients and seven multiparous sectioned patients were delivered of larger infants at the subsequent vaginal deliveries than the original section deliveries. There were 106 vaginal deliveries following the 62 sections. The fetal deaths were three, all nonpreventable (an intrauterine death before labor, an 8 weeks premature infant with hydrops fetalis, and a 10 weeks premature, 3 pound, 1½ ounce infant).

The danger of rupture of the uterus complicating an attempted vaginal delivery is admitted and discussed.

Conclusion

A trial of labor seems indicated as the management of choice in a certain number of properly evaluated patients, when supervised by a competent obstetrician in a hospital equipped to meet all emergencies. The significance of successful vaginal delivery following cesarean section has been stressed. Thus, the old dictum "Once a cesarean section, always a section," should be changed to "Once a cesarean section, not necessarily always a cesarean section."

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DYSGERMINOMA OF THE OVARY*

An Analysis of 17 Cases With Special Reference to Histogenesis and Therapy

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DYSGERMINOMA is an epithelial neoplasm which, though morphologically malignant, has been considered, heretofore, relatively benign and less malignant clinically than the granulosa-cell carcinomas. It is identical in structure to the seminoma occurring in the testis. Several designations for this tumor have been used in the past, such as small- and large-cell carcinomas, embryonal-cell carcinoma, seminoma, and others. Today the name dysgerminoma, first introduced by Robert Meyer,[1] is commonly used.

The incidence and the degree of malignancy will be further clarified as more cases are reported. The present series of 17 cases collected from 1926 to 1949 is one of the largest yet studied. Of these, 15 patients were observed at the Jewish Hospital of Brooklyn and 2 at the University Division of Kings County Hospital.

Pathology

The tumor is usually unilateral. Thus only two in this series were bilateral, the remainder being almost equally divided between the right and left ovaries. It varies in size from 3 to 5 cm. in diameter to a large mass filling the entire pelvis. The smallest tumor here reported was 11 cm. in diameter. Early in its development the tumor is covered by a fibrous capsule which disappears in later stages when perforation has occurred. The tumor retains the shape of the ovary and may have knobby excrescences. It is rubbery in consistency, and when large is soft and friable due to extensive necrosis. On cut section, the surface is grayish pink with areas of degeneration, necrosis, and hemorrhage. Cystic degeneration is rare.

The microscopic picture is very distinctive and characteristic. The cells comprising the tumor are large, round, or polygonal in shape, with abundant clear cytoplasm and a large centrally placed nucleus. They are arranged in alveoli separated by strands of fibrous tissue that show hyalinization and round-cell infiltration. Mitotic figures are not uncommon. Some tumors are highly cellular and have few fibrous septae while, in others, the fibrous septae are more prominent. Areas of degeneration and hemorrhage are common. In the areas of degeneration large giant cells similar to those seen in tuberculous lesions are found. This was noted by Schiller[2] to be fairly common. This tumor has been found in association with teratomas and choriocarcinoma.

Metastases occurred through the lymphatics and by direct continuity to adjacent organs when the capsule perforated. Other metastases were general-

*Presented at a regional meeting of the Brooklyn and Long Island Chapter of the American College of Surgeons at Kings County Hospital, Jan. 14, 1950, and at the Brooklyn Gynecological Society, Jan. 17, 1951.

TABLE I

NO. OF CASES	LOCATION			SIZE			METASTASES	
	RIGHT	LEFT	BILATERAL	LESS THAN 10 CM.	GREATER THAN 10 CM.	FROZEN PELVIS	AT OPERATION	POST-OPERATIVE
17	8	7	2	0	16	1	6	11

ized and involved organs outside of the abdominal cavity such as the heart, lungs, or thyroid gland, etc., apparently entering and spreading through the systemic circulation. An interesting finding at autopsy in four of our cases was the occurrence of hydroureter and hydronephrosis due, probably, to involvement of the periureteral nodes and parametrium compressing the ureter. This finding was also reported by Wolfe and Kaminester[3] in one of their cases.

Bilateral dysgerminomas may represent either two primary tumors or a metastasis in one from a primary tumor in the other by retrograde lymphatic spead. Thus, in the cases where the tumor was present in both ovaries the downhill course was more rapid and severe (Fig. 1).

Fig. 1.—Photograph of autopsy specimen of uterus and other ovary containing metastatic tumor. Note that the ovary is encapsulated and retains its general shape. At operation 3 months previously this ovary was normal in size and appearance.

In this series there was one case of choriocarcinoma within a dysgerminoma and a similar case has come to our attention by personal communication.[4] In both the Aschheim-Zondek tests were positive in dilutions, thus indicating that these tumors elaborated a gonadatropic hormone. Barzilai[5] stated that although neither male nor female sex hormones have ever been demonstrated in the tumor itself nor in the body fluids of these patients, there exist sufficient pituitary-like hormones to give a positive Aschheim-Zondek test. Salmon, quoted by Geist,[6] isolated a gonadotropic hormone from a dysgerminoma. Burge[7] reported two cases of ovarian dysgerminoma associated with positive Aschheim-Zondek tests, in spite of proved absence of gestation or choriocarcinoma. Recently a

seminoma of the testes came to our laboratory in which the Aschheim-Zondek test was positive and sections from the tumor failed to reveal chorionic tissue. Thus, the male counterpart may produce the gonadotropic hormone.

The exact cell origin of this tumor is still a moot question and, at the present time, no one can make arbitrary and definitive statements in this regard. The most commonly accepted theory is that of Robert Meyer who postulated that the tumor is composed of sexually undifferentiated cells similar to those seen in the undifferentiated stage of gonadal development. This is further supported by the finding of similar tumors in the male testis (seminoma). On the other hand, Pick,[8] Ewing,[9] and Wolfe and Kaminester[3] believed that the cell of origin belongs to the sex cell series and arises from a totipotent cell close to the ovum. They were further influenced in this belief by the presence of chorio-carcinoma and other teratomas within some of these tumors. These findings, however, cannot be adequately and satisfactorily explained by Meyer's theory except by postulating that these represent two separate coincidental tumors from different cell origins.

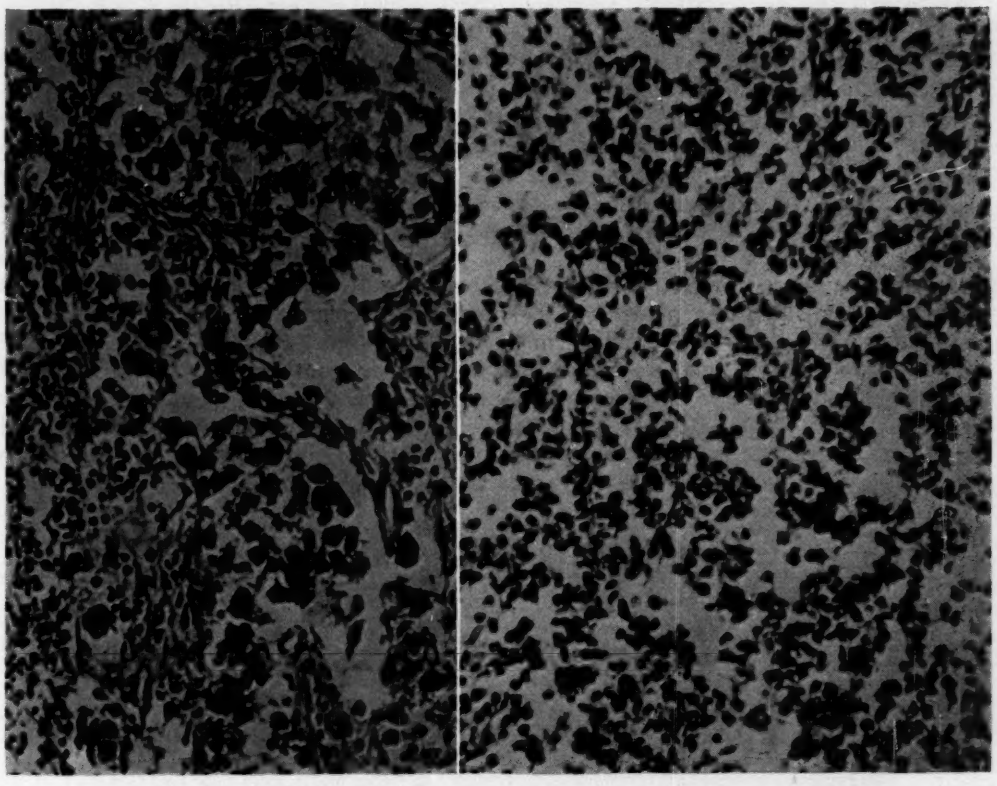

Fig. 2. Fig. 3.

Fig. 2.—Photomicrograph of tumor showing alveolar pattern and lymphocytic infiltration of the stroma.

Fig. 3.—Photomicrograph of tumor showing more marked cellularity and a scanty stroma.

In an analysis of 922 testicular tumors, Friedman and Moore[10] found the presence of trophoblastic tissue within many of the embryonal carcinomas. Cytotrophoblastic tissue was present in greater frequency than syncytiotrophoblastic tissue, the latter being found only in focal areas. Chorionepithelioma

was present in 6 per cent of the cases. These elements were found in metastases, despite the fact that they could not be demonstrated in the original tumor. These authors felt that embryonal carcinoma arose from totipotent cells (Fig. 7).

In the case of dysgerminoma described by personal communication,[4] chorionepithelioma was found in the metastases shortly after the primary operation, despite the fact that no such tumor was found in the ovary. Thus, in both embryonal carcinoma of the testis and dysgerminoma of the ovary, chorionepithelioma can appear in metastases without being noted in the original tumor. The conclusion, therefore, is almost inescapable that these tumors arise from totipotent cells.

TABLE II. SITES OF METASTASES

Ovary	7	Kidney	1	Pancreas	1
Uterus	6	Heart	2	Abdominal scar	2
Lymph nodes	7	Thyroid	1	Peritoneum	7
Pleura and lungs	3	Diaphragm	1	Gall bladder	2
Spleen	4	Intestines	3	Omentum	4
Liver	4	Adrenal	1		

We believe that this tumor arises from totipotent cells of the primitive gonadal mesenchyma capable of differentiating in any direction. This tissue gives rise to both the epithelial and the nonepithelial or connective tissue components of the gonads in both the male and the female. The direction of differentiation of the cells will ultimately determine the nature of the tumor. Thus, in the female, if growth is along the male line, the arrhenoblastoma will result, while growth along the female line produces either the thecomas or granulosa-cell tumors. However, if the growth is from neuter cells, the dysgerminoma will result. In the male, the same cell gives rise to the seminoma. As a rule the cells are neuter as far as producing either male or female sex hormones. Yet occasionally an anterior pituitary-like hormone is produced. Seminoma of the testis may also react in a similar manner. Moreover, Babes,[11] Reifferscheid,[12] and Schiller[13] have each reported mixed tumors composed of granulosa-cell tumors and dysgerminomas which further supports the origin of these tumors from the same totipotent mesenchymal cell. Thus it is not surprising to find teratomas and choriocarcinomas associated with this group of tumors since these totipotent cells give rise to these tumors also (Table III).

TABLE III. HISTOGENESIS OF MIXED TUMORS FROM THE TOTIPOTENT CELL. OTHER MIXED TUMORS ARE THEORETICALLY POSSIBLE

		MIXED TUMORS REPORTED TO DATE
Totipotent cell	Thecoma	Granulosa-cell carcinoma Thecoma
	Granulosa-cell carcinoma	Granulosa-cell carcinoma Dysgerminoma
	Dysgerminoma	Dysgerminoma Teratoma
	Arrhenoblastoma	Dysgerminoma Chorionepithelioma
	Teratoma	Arrhenoblastoma Teratoma
	↓	
	Chorionepithelioma	

Clinical Picture

Although published reports reveal this tumor to be one-third as common as granulosa-cell tumors, in this series dysgerminoma was almost twice as common as the latter. Although this tumor is commonly believed to occur in early

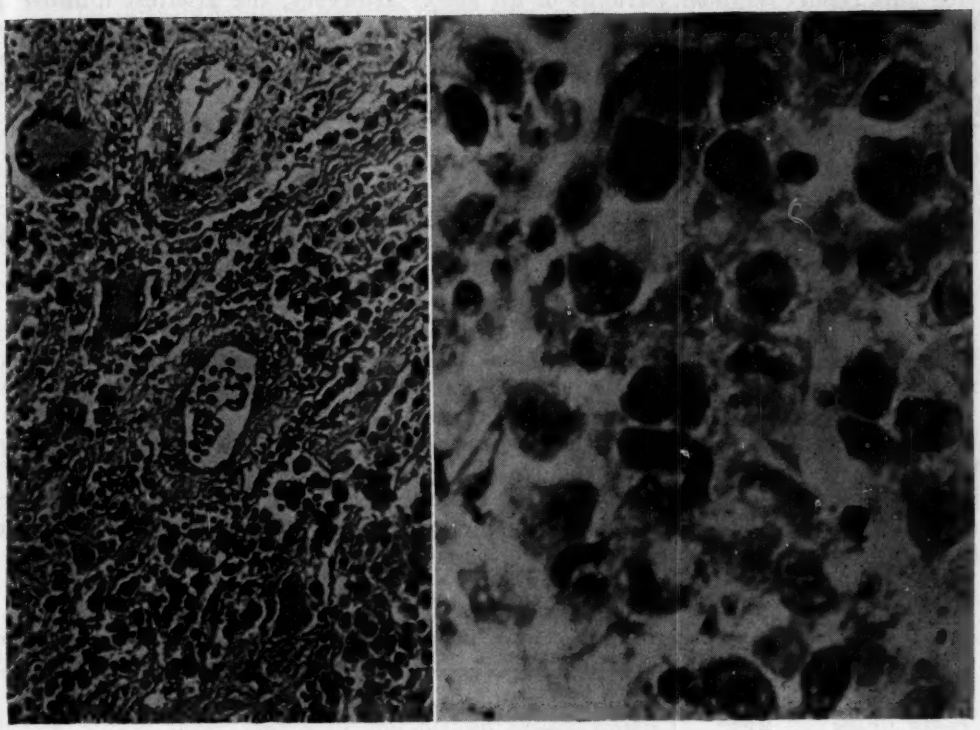

Fig. 4. Fig. 5.

Fig. 4.—Photomicrograph showing giant cells and hyalinization of the fibrous stroma.
Fig. 5.—Photomicrograph of the tumor under higher magnification. Note mitoses.

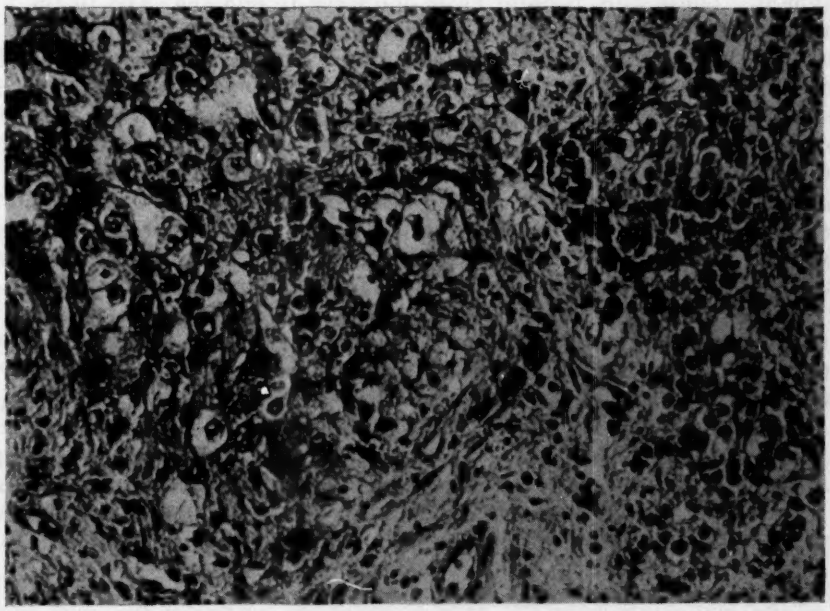

Fig. 6.—Photomicrograph of junction of dysgerminoma and choriocarcinoma in same tumor. (From the private files of Dr. Irwin Neigus.)

life, this report includes patients of all ages. However, the greatest number of cases was noted in the first three decades of life. The youngest patient was 6 years old, while the oldest was 78 years old (the oldest case on record) and the average was 31 years. Moreover, 5 were in prepuberty and early adolescent life, 8 were in the active sex life, and 4 were postmenopausal.

TABLE IV

NO. OF CASES	AGE IN YEARS								
	5-10	10-15	15-20	20-30	30-40	40-50	50-60	60-70	70-80
17	3	2	2	4	2	0	1	2	1

While dysgerminoma has been described as being associated with pseudohemaphroditism, sexual maldevelopment, and menstrual abnormalities, this was not the finding in this series where all patients were normal physically. One 13-year-old child had marked mental retardation.

Conception has occurred in the presence of these tumors and, moreover, has followed the conservative removal of the tumor. Of these 17 patients, 7 bore one or more children prior to the discovery of the tumor, but none afterwards. This may be explained by the fact that those who survived to date had their families prior to surgery except for two who are still unmarried.

TABLE V

NO. OF CASES	SYMPTOMS			DURATION				ASCITES		
	PAIN	ABDOMINAL ENLARGEMENT	ASYMPTOMATIC	1 WEEK	1-3 MONTHS	3-6 MONTHS	6 MONTHS 1 YEAR	PREOP.	POSTOP.	BLOODY
17	15	15	1	3	8	2	3	6	3	4

No characteristic symptoms are associated with this tumor. However, with increasing size of the tumor vague abdominal complaints of a chronic nature are common. These were present from one week to one year and in the majority of cases were present from one to six months prior to surgery (Table V). Abdominal pain and enlargement were the two common symptoms which brought the patient to the doctor. These were associated with recurrent attacks of nausea and vomiting. The tumors, as a rule, grow rapidly to a relatively large size, outgrowing the blood supply and thereby undergoing necrosis. Involvement of the serosa produces an irritative peritonitis, and causes pain, nausea, and vomiting. These symptoms were present in all but 2 cases. Torsion of the pedicle with symptoms of an acute abdominal crisis may occur, as was found in 2 of our cases. One tumor was discovered during a routine examination while, in the other, the enlargement was due to a painless ascites (in the latter case, the mass was discovered following the paracentesis). In 6 cases, ascites was present prior to or at operation and varied in amount up to 6 liters. In 4, the fluid was hemorrhagic, indicating a poor prognosis which was confirmed by the subsequent course. In 3 other cases, the ascites developed following operation. Our longest survivor had clear ascitic fluid at operation. In one of our cases, the symptoms simulated acute appendicitis and the patient was operated upon for this condition and the true nature was not recognized at this time. Seven months later, the patient was admitted to our institution because the pains persisted despite the appendectomy. Examination revealed the presence of an abdominal mass which proved to be a dysgerminoma. All such patients should have rectal or pelvic examination and inspection of pelvic organs at time of laparotomy. In 6, metastases were present at primary operation. Of these, 3 were solitary and 3 were generalized.

The only laboratory test of diagnostic value is the Aschheim-Zondek test, which, if positive, may help in the diagnosis. If pregnancy is suspected, a flat plate of the abdomen will usually rule out a gestation greater than 14 weeks. Young individuals with solid ovarian tumors should routinely have an Aschheim-Zondek test done, which, if positive, may prove to be of great diagnostic import in helping to make the diagnosis preoperatively of such tumors. It must be borne in mind, however, that this test rapidly becomes negative after removal of the tumor. In one case, although the Aschheim-Zondek test had been positive in dilutions up to 1:100, it was negative on the eighth postoperative day.

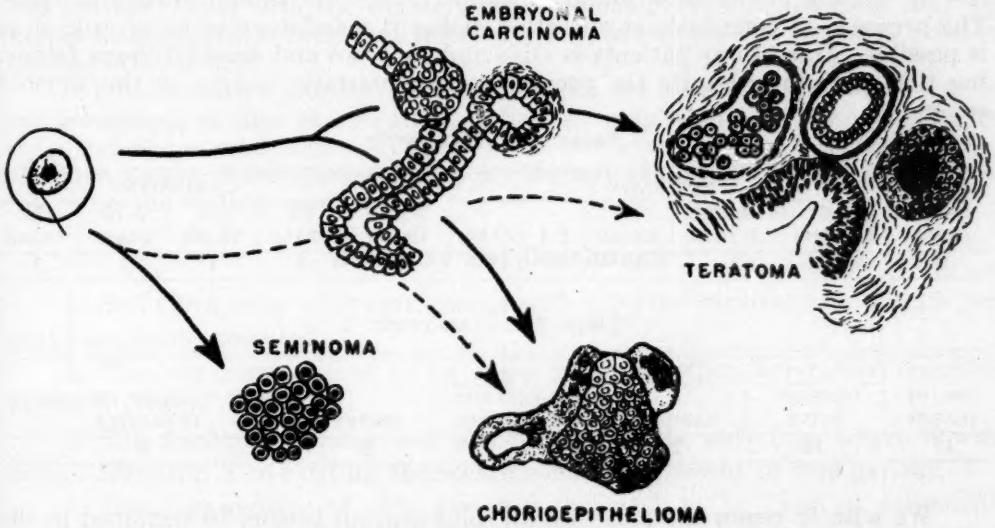

Fig. 7.—Schematic representation of lines of development of testicular tumors (by courtesy of Drs. N. B. Friedman and R. A. Moore).

The true degree of malignancy of these tumors has not yet been definitely established. Döderlein[14] reported the death rate to be 18.8 per cent; Novak[15] 24.5 per cent, while at the Mayo Clinic, the death rate was about 40 per cent based on 5-year cures. Mueller, Topkins, and Lapp,[16] in a review of the literature of cases with follow-up, found a 5-year cure rate of 27.3 per cent and a 15-year cure rate of 4.8 per cent. In our series, 2 patients are alive 5 years or more with the longest survival of 16 years. Three others are alive and well since operations from one to two and one-half years, respectively. The latter had a solitary metastasis involving the sigmoid colon. One died from peritonitis on the nineteenth postoperative day. Ten died within one year and of these 7 within 6 months. In the latter group, 5 had metastases at the primary operation. One lived for 3 years and 10 months. Autopsies were performed on six of the above 12 patients and 5 revealed generalized metastases while the sixth presented a generalized peritonitis without any metastases. The death rate was 70.6 per cent and to date the 5-year survival rate is only 12.5 per cent and the 15-year survival rate is 5.9 per cent. This degree of malignancy is greater than that previously reported and should call attention to the fact that this tumor is potentially more malignant than heretofore considered (Table VI).

Treatment

Since the vast majority of patients with dysgerminoma are either young girls or women in the active sex life, one is faced with the choice of choosing between the conservative or the radical approach to the problem. In the former,

salpingo-oophorectomy, both the menstrual and the childbearing functions are preserved, whereas in the latter approach, a total hysterectomy with bilateral salpingo-oophorectomy, these functions are sacrificed. If the mass is encapsulated, and with no apparent metastasis present, the vast majority of physicians advocate a simple salpingo-oophorectomy. On the other hand, metastases may be present even though not found at operation. These may be found only if the broad ligament and lateral pelvic walls are palpated at operation, and the broad ligament examined microscopically. This should be done in all cases and a radical procedure performed if metastases are found. However, in those patients who have already acquired their families, or are postmenopausal, regardless of the size of the mass found, a radical procedure should always be done. The presence of metastasis at operation makes it mandatory to be as radical as is possible. One of our patients is alive and well two and one-half years following this procedure despite the presence of a metastatic nodule on the sigmoid colon.

TABLE VI. FOLLOW-UP

	MORTALITY					SURVIVAL			
NO. OF CASES	1-6 MONTHS	6 MONTHS-1 YEAR	1-2 YEARS	2-4 YEARS	NO. OF CASES	1-2 YEARS	2-5 YEARS	5-10 YEARS	15+ YEARS
12	7	3	1	1	5	2	1	1	1

TABLE VII. TREATMENT

	OPERATION				
NO. OF CASES	CONSERVATIVE	RADICAL	CONSERVATIVE AND RADICAL	BIOPSY	X-RAY THERAPY FOLLOWING OPERATION
17	12	2	1	2	6

We wish to renew the plea that all solid ovarian tumors be sectioned in the operating room so as to evaluate the tumor properly and guide the operator in the procedure he will follow. Thus, secondary operations may be avoided, as was necessary in one of our cases, when the true nature of the tumor is recognized at the time of operation.

Although these tumors are believed to be radiosensitive, this therapy was disappointing in those patients who received such treatment. Four apparently were adequately treated, yet three died within one year and one lived for three years and ten months. Two others had treatment started when the process was far advanced and succumbed before they had been adequately treated. Despite this, radiotherapy should follow radical surgery and conservative treatment also, if metastases later become evident. Occasionally inoperable cases become amenable to surgery following x-ray therapy.

It is interesting to note that one of our patients developed dysgerminoma 17 years following a successful x-ray-induced menopause for menorrhagia. This would indicate that although follicular activity was destroyed, the embryonal mesenchymal cells were probably not completely eradicated or affected.

Comment

In our series, conservative therapy was followed, in the vast majority of the cases, yet the mortality was high. There were 8 patients, all in the younger age group, treated conservatively who had no apparent metastases at operation. Four of these developed metastasis within 6 months following operation, 2 of whom received, also, x-ray therapy shortly after the operation, thus nullifying the prime purpose of conservative therapy. All of these 4 succumbed within a relatively short time. Another died of peritonitis postoperatively. Two other

patients, in the postmenopausal group, were dead within 6 months. Childbearing and menstruation have been preserved in 3 patients, 16 years, 6 years, and 1 year, respectively, following operation. One of the 3 patients had a family prior to surgery. If radical surgery had been done in all the patients, our 5-year survival rate might have been increased greatly, although childbearing would have been destroyed in only 2 cases.

In view of the malignant nature of the tumor with its high mortality, it is our feeling that it would be wiser to employ radical surgery in all patients regardless of age, size of the tumor, and its degree of encapsulation. This procedure will destroy the above-mentioned functions in some who might have had similar results with the conservative treatment. Yet, in the long run, we would rather sacrifice these functions in a few in the hope of saving a greater number of patients.

If a conservative procedure is done because the true nature of the tumor is not recognized at time of operation, radical surgery should be done as soon as the diagnosis is established. This is to be preferred to x-ray therapy alone, although we are of the opinion that x-ray therapy should be given to all patients following the radical operation.

Summary and Conclusions

1. Seventeen cases of dysgerminoma with a 5-year survival rate of 12.5 per cent have been presented.

2. The tumor was found to be more malignant than heretofore reported in the literature.

3. The Aschheim-Zondek test was positive in the only case where it was done. However, a co-existing choriocarcinoma was present in this patient.

4. The histogenesis of this tumor is believed to be from a totipotent primordial mesenchymal cell capable of differentiation in all directions, thus accounting for the presence within such tumors of choriomatous and teratomatous tissues.

5. Tumors may show choriomatous elements in the metastases although they are not demonstrable in the primary tumor itself.

6. Similar findings have been reported in the embryonal carcinoma (seminoma) of the tests.

7. Radical surgery is advocated, where feasible, in all the patients, regardless of age, size of tumor, and degree of encapsulation, to be followed by x-ray therapy.

8. Histological examination should also include the broad ligament and the mesovarium for possible lymphatic involvement indicating spread of the tumor despite an intact capsule.

We wish to thank the members of the gynecological and obstetrical departments for the use of cases from their services and private files.

We wish also to thank Drs. S. A. Wolfe, Morris Glass, and Louis M. Hellman for their constructive criticisms.

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PROLONGED LABOR: ITS CLINICAL RECOGNITION AND MANAGEMENT*

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THE remarkable advances in our knowledge of the physiology of pregnancy, and our ability to prevent and control infections and to replace lost blood have steadily reduced both maternal and fetal mortality, but the problem of protracted labor has yet to be solved. The woman whose labor is so abnormal that she is unable to deliver her infant within 24 hours is subjected to an increasing incidence of injury, hemorrhage, or infection and her child is less likely to be born alive and healthy. Prevention of abnormal labor obviously would make the treatment of its complications unnecessary, hence the ultimate goal is to eliminate the responsible factors. Current investigations of the physiology of the normal uterine contractions and their alteration in abnormal states will provide us with an exact analysis of the deficiencies of the mechanism in protracted labor from which may evolve a physiological method for its correction. In the meantime, we must cope with the problem as well as we can, aiming to prevent abnormal labor if there are preventable factors and if not to make such labors as atraumatic for both mother and infant as is possible. In an effort to determine the results of our management of patients in prolonged labor and to analyze our errors, the records of the 118 patients discussed here were reviewed.

Material

Between Jan. 1, 1947, and Jan. 1, 1950, 6,723 patients were delivered on the obstetrical division of the Temple University Hospital. The 118 patients reported here represent 1.8 per cent of the entire group and were selected because in each the labor extended over at least a 24-hour period and in none of them was disproportion thought to be a primary factor in the delay. One hundred one were primigravidas and only 17 were multiparas. Of the former, 7 were over 35 years of age and 56 over 25. Labor began between the thirty-eighth and fortieth weeks of gestation in all except 2, who were 37 weeks pregnant, and in only 3 was it induced. Each patient was checked carefully during labor, almost all being constantly attended by a senior medical student or an intern, who made and recorded observations of blood pressure, pulse rate, interval between and duration of contractions, and fetal heart tones, at least twice an hour during the first stage and more frequently after the cervix became completely dilated. The findings were checked at intervals by the obstetric resident and since consultation is required in all cases of prolonged labor each patient had the additional advantage of evaluation by one of the senior obstetricians.

*Presented at a meeting of the Philadelphia Obstetrical Society, Dec. 7, 1950.

The time of the onset of labor was sometimes difficult to determine with accuracy but no patient was considered to be in labor unless her uterine contractions were productive of progress: i.e., descent of the presenting part and/or effacement or dilatation of the cervix. The longest labor recorded in the group was 68½ hours, 14 labors lasted longer than 40 hours, and 56 longer than 33 hours.

In 8 instances the breech was the presenting part and in 1 the face; there was 1 set of twins and in the remainder the vertex presented. Of the latter group 42 were occiput anterior positions, 25 occiput transverse, and 29 occiput posterior at the time of delivery. In 12 the position was not clearly indicated.

Although 6 patients were considered to have had slightly reduced measurements, in no instance was the pelvis considered to be a significant factor in the delay. It is likely that in some there existed unrecognized cephalopelvic disproportion as indicated by the size of the infant and excessive molding of the head, but we believe that in almost every case a faulty mechanism was the important factor which prevented normal termination. The evidence for this statement is suggested by clinical evaluation of the uterine contractions which seemed primarily responsible for the failure to progress. In only 38 patients did the contractions at any time during labor occur regularly and at less than 4-minute intervals, while in the remainder they were irregular both in interval and duration with frequent periods during which little or no uterine activity was discernible. In 53 the duration never exceeded 45 seconds, and it often was noted on the record that the contractions were weak or that the uterus could be indented at the height of a contraction.

In 21 the membranes ruptured spontaneously before the onset of labor and in all but 4 labor began within 24 hours; the longest latent period was 6 days. In none of these patients did labor ever assume a normal character. Five of the 21 had febrile puerperia, 4 from endometritis and 1 from pyelonephritis. In each instance the morbidity occurred in those with short latent periods between rupture of the membranes and the onset of labor. The membranes were ruptured artificially during the first stage 46 times in an attempt to facilitate labor and in 27 others spontaneous rupture occurred before the cervix was completely dilated. Almost no effect was noted on the efficiency of the contractions or the course of the labor, again evidence of the unusual mechanism in progress.

Only 11 patients were given oxytoxic drugs during labor and in each instance Pitocin was used either by intermittent intramuscular injection in ½ to 1 minim doses or intravenously as a continuous drip, 10 minims of Pitocin being added to 1,000 c.c. of 5 per cent glucose and allowed to flow at a rate of about 200 c.c. per hour. In 8 there was either a questionable response or none at all and in 3 the contractions and the remaining labor became more normal.

The types of delivery are summarized in Table I. It will be noted that the incidence of midforceps deliveries and of rotations both at the midpelvis and below was definitely increased over that of a normal group of patients. The most common indication for terminating labor was cessation of progress with increasingly abnormal contractions which no longer improved after rest and hydration. In a few, early intrauterine anoxia as evidenced by slight alterations in fetal heart rate prompted delivery, but in none were the fetal heart sounds alone used as indications for major operative interference.

In 25 patients it was thought necessary to terminate the labor before complete dilatation of the cervix had been attained but in only 1, with fibrosis following an extensive conization, was the cervix considered to be the major factor in the delay. In 17 it was felt that the infant could safely be ex-

tracted vaginally and in these the cervix was incised 13 times and manually "dilated" in 4 others; in each of the latter only a rim of cervix remained. Delivery was accomplished by midforceps extraction in 15, breech extraction in 1, and low forceps in 1. In each instance the presenting part was below the spines and vaginal delivery was chosen because the pelvis was considered to play no part in the delay and abdominal delivery was not thought to have been necessary.

TABLE I. METHOD OF DELIVERY

Spontaneous			4
Low, outlet forceps	Simple	42	
	With rotation	17	59
Midforceps	Simple	6	
	With rotation	32	38
Breech	Spontaneous	1	
	Extraction	7	8
Cesarean section	Lower segment	1	
	Extraperitoneal	7	8
Version and extraction		1	1
Total			118

The incidence of postpartum hemorrhage in patients with prolonged labor is increased because of uterine atony and injury. In addition the total hemoglobin loss associated with hemorrhages of equal volume may be greater in patients after prolonged than after normal labor because of dehydration and hemoconcentration. In 15 patients, or 12.7 per cent, the estimated blood loss was 500 c.c. or over, the maximum being 1,500 c.c. Eleven of the hemorrhages were thought to have resulted from uterine atony, 1 from retained placenta fragments, and 3 primarily from the episiotomy or from vaginal injury, although there also were vaginal tears or extension of the episiotomy in 2 of those whose uteri failed to contract properly. Fourteen were delivered by midforceps extraction and 1 by version and extraction under deep anesthesia. The placenta was removed manually 20 times after failure of expression in order to empty the uterus to allow it to contract properly.

TABLE II. MORBIDITY AND PROPHYLAXIS IN LABOR

	FEBRILE	AFEBRILE	
Penicillin, sulfonamide or both, 39 patients.—	Endometritis	5 (13%)	
	Pyelonephritis	3 (8%)	30 (77%)
	Wound	1 (3%)	
None, 79 patients.—	Endometritis	8 (10%)	
	Pyelonephritis	7 (8%)	60 (76%)
	Wound	1 (1%)	
	Unknown	3 (4%)	

A febrile puerperium (100.4° F. in any two 24-hour periods except the day of delivery) was experienced by 28, or 24 per cent, of the patients. Since it is our custom to record temperatures four times daily on all normal puerperal patients and six times on the abnormal ones it is unlikely that any morbidity was overlooked. Only 19 per cent of the 31 Negro patients were febrile as compared with 30 per cent of the white women. When broken down into ward and private patients, the figures are 21 per cent and 26 per cent, respectively. This reversal of the usual findings is difficult to explain since all were managed by the same staff in much the same manner. There was no obvious difference in method of delivery or treatment during labor to account for the results.

The site of infection was the uterus in 13, the urinary tract in 10, the episiotomy in 1, and the abdominal wound in 1; in 3 others the cause was obscure. None of the patients with fever was seriously ill. In 6 of those with endometritis the placenta had been removed manually but the procedure was not thought to have been responsible, since it was not followed by infection in others in whom it was carried out and since we rarely encounter infection after invasion of the normal uterus either to remove the placenta or for exploration. Sixteen of the febrile patients had had major operative deliveries, 11 midforceps extractions, 3 cesarean sections, and 2 breech extractions. Of those delivered by midforceps in 9 it had also been necessary to incise the cervix. An attempt was made to relate the morbidity to the length of labor, the number and type of examinations, the administration of fluids, and to the prophylactic use of antibiotic and chemotherapeutic agents (Table II), but no definite conclusions could be drawn. No patients developed thrombophlebitis or pulmonary embolism and there were no maternal deaths.

There were 5 fetal deaths, 4 of them undoubtedly attributable to the protracted labor.

1. A 9 pound, 12 ounce, white infant was delivered by breech extraction after 43 hours of labor during which no fluids or antibiotics were given. The infant died after delivery of pneumonia which undoubtedly was contracted in utero. The mother's puerperium was uncomplicated.

2. A 6 pound, 5 ounce, Negro infant was delivered by an easy low forceps rotation from an occiput left transverse position after a 52-hour labor. The baby died of intracranial hemorrhage.

3. A 6 pound, 6 ounce, white infant died during a labor which terminated after 29 hours, 45 minutes. The mother who had had adequate fluids but no antibiotics during labor developed endometritis. No autopsy was permitted on the infant and an unequivocal cause of death could not be assigned.

4. A 6 pound, 5 ounce, stillborn Negro infant was delivered by outlet forceps after a 31 hour, 28 minute labor. The mother had received no antibiotics or fluids during labor and developed endometritis. Autopsy showed only aspiration pneumonia.

5. A 12 pound, 7½ ounce, stillborn white erythroblastotic infant was delivered by breech extraction after 37 hours and 48 minutes of labor.

Two of the infants who failed to survive had pneumonia and in neither instance was treatment administered to the mother during her labor; these therefore are at least potentially preventable fetal deaths. Another died from intracranial hemorrhage which seemed unlikely to have been due to the uncomplicated low forceps delivery but which must in any event have resulted from the abnormal labor.

We were unable to substantiate the concept that the lowest infant mortality rate can always be achieved by allowing labor to continue to spontaneous or low forceps delivery since 1 infant died during labor, 1 was delivered by outlet forceps and another by an easy low forceps rotation from a transverse position. The remaining baby was born by breech extraction after prolonged delay in the second stage and a period of time more than adequate to demonstrate the impracticability of further procrastination.

In addition to the deaths, 5 infants suffered some form of obvious injury: of 3 with signs of mild intracranial hemorrhage all recovered without demonstrable residual damage; 1 had a mild transient brachial plexus injury, and 1 a temporary facial palsy. The 3 infants with intracranial hemorrhage presented as breeches and the others were delivered by midforceps extraction. Thirty-four babies required resuscitation.

Of the 119 infants, 31 weighed over 8 pounds, 8 of them over 9 pounds. The large proportion of infants (40) weighing less than 7 pounds of this group of patients delivered at term can be accounted for by the number of Negro patients whose babies are likely to be somewhat smaller than the accepted average.

Comment

The results of the management of the patients presented here again demonstrate the increased maternal and fetal morbidity and fetal mortality if labor extends beyond the normal period of time. Since the risk to the patient and the infant is increased, early recognition and definitive management directed toward the encouragement of normal contractions, the prevention of infection and dehydration, the protection of the infant, and the early detection of any change suggesting the need for termination are important.

Frequently such a labor may be prognosticated from the fearful reaction of the patient toward her pregnancy and considerable time should be spent during the prenatal period preparing her for delivery. In some the fears are simple and easily detected but in others they are less obvious.

At the onset of normal labor the contractions may occur as far apart as 10 to 30 minutes but rather rapidly the interval diminishes and the duration increases until they recur about every 2 minutes and last 90 seconds. During the height of a contraction the upper part of the uterus is hard and cannot be indented and muscular relaxation between contractions is complete. In the normal primigravida we expect cervical dilatation and descent to be progressive and delivery to occur in about 12 hours. Some of the patients who will have inert labors start much like the normal but the progression to regular firm effective contractions does not follow. Subjective reaction is a poor criterion as to the normalcy of labor since the response to pain may be exaggerated in these patients. The only clinical method for the elevation of uterine activity, except for progression of labor, is to sit at the bedside with the hand on the uterus and palpate a series of contractions. The frequency and duration, as timed by the clock, the firmness of the upper segment and the relaxation between contractions all should be noted and recorded. If after such evaluation it is suspected that a poor mechanism is present or will develop the patient is considered as a candidate for prolonged labor and is managed as such from the onset.

The administration of the usual analgesic drugs during true labor has little effect upon the efficiency of the uterus, in fact, labor frequently improves after sedation because psychological inhibition is reduced. In the patient with a poor mechanism, however, normal amounts of sedation may inhibit the contractions completely and therefore the program for pain relief must be altered. If the first sedation in a patient whose labor appears to be normal is followed by more than a temporary decrease in the frequency or duration of the contractions, it is likely that some defect exists and subsequent attempts to relieve pain are carried out as for the patient during an inert labor. If the contractions are short, irregular, and of poor quality, no attempt is made to produce analgesia or amnesia in the usual sense of the terms; rather such patients are given intermittent periods of heavy sedation which will completely relieve pain and allow them to rest and sleep. Six to 8 hours' sleep out of each 24 hours of labor are desirable and may be obtained by the injection of morphine sulfate 0.010 to 0.016 Gm. about every 6 hours. In most instances after morphine the patient will rest well for 2 to 3 hours, but, if she does not sleep, despite the pain relief, Nembutal or Seconal, 0.2 Gm., may be

required in addition to the analgesic preparation. Of course one must feel certain that delivery is not imminent if heavy sedation is administered. If sedatives are properly utilized the patient can be brought to delivery even after a markedly prolonged labor rested and in good condition.

The combination of protracted labor, restlessness of the patient, and a low fluid intake may occasionally produce severe but unnecessary dehydration. At least 2,000 c.c. of fluid in each 24 hours of labor are desirable unless the environmental temperature is high or the patient has fever, in which event it must be increased. The normal reduction of gastric emptying time during labor is exaggerated by sedation, and since there may in addition be vomiting oral fluids are given in limited amounts and cannot be relied upon to supply an adequate intake, hence 10 per cent dextrose in distilled water is administered intravenously at intervals during labor. The slightly concentrated solution is used because of its sugar content and is given slowly so both the glucose and the fluid will be utilized by the depleted tissues and dehydration will not be increased. The fluid usually is administered in units of 1,000 c.c., or more if indicated, during the rest periods when the patient is quieted by sedation.

Crystalline procaine penicillin is injected intramuscularly in 300,000 unit doses every 12 hours, the first dose being given as early as prolongation of labor is suspected; in addition sodium sulfadiazine, 2.5 Gm., is given intravenously in the glucose at least twice in each 24 hours of labor. The combination of drugs being effective against a wider range of organisms offers more complete protection for both mother and infant than does either one alone. It is inevitable that in some instances the drugs are administered to patients whose labors terminate in less than 24 hours and are withheld too long from others.

A common but understandable error is overexamination. Since rectal examinations are not only uncomfortable but potentially dangerous from the standpoint of introducing infection into the uterine cavity they are limited as much as possible. Few of these women will precipitate and in almost every instance descent can be followed by abdominal palpation of the cephalic prominence or the shoulder, palpation through the perineum for the presenting part, or simply visualization of the perineum for bulging. Determination of dilatation and station more exactly before the administration of sedation is desirable and for this purpose rectal examination usually is satisfactory.

Each patient should have at least one sterile vaginal examination made by a capable obstetrician early in the course of prolonged labor in an effort to evaluate the pelvis, to detect abnormalities in position, and to determine the station and the condition of the cervix. Certainly another such examination should be made before abdominal delivery is resorted to, if there is evidence of fetal distress or if the findings on rectal examination are not conclusive.

There is infrequently an indication for x-ray pelvimetry and the necessity is rarely present unless the patient is in labor; x-rays at this time, particularly in abnormal labor, may be of great value in detecting mild disproportion or abnormal positions not easily demonstrable by clinical examination alone. One of their important uses is in determining whether apparent descent of the presenting part is the result of true progress or of caput formation; the latter can be suspected clinically, however, if the cephalic prominence remains stationary and the head appears to descend through the pelvis on rectal examination. A true evaluation of engagement of the presenting part and the architecture of the pelvis as demonstrated by roentgenograms may at times be of utmost value in the decision as to whether vaginal or abdominal delivery is to be undertaken.

Rupture of the membranes usually hastens labor and it is our custom to consider their artificial puncture at the time of diagnostic vaginal examination in those patients whose labor is progressing slowly and in whom the cervix is partially dilated and the vertex well fixed in the pelvis. This procedure often is followed by improved contractions and many patients are not included in this report because artificial or spontaneous rupture of the membranes allowed the labor to terminate promptly and within the time period considered to be normal. That this is not always effective, however, is demonstrated in the patients here reported in whom little difference was noted in the labor after the bag of waters ruptured, again pointing to the inherent difference in the uterine mechanism between this group and the normal.

Pituitrin was resorted to only occasionally and its results were not startling. In a few the contractions improved but in general it added little to the treatment of these labors. Others have reported its successful use,[1, 2] particularly when given early, and we have a small group of patients not included in this report in whom an intravenous drip of Pitocin has been used to induce labor or who were in potentially protracted labor and in whom the contractions improved and normal delivery occurred following its administration. If the poor mechanism can be detected early and cannot be corrected by such measures as rupture of the membranes, if there is no suggestion of cephalopelvic disproportion or of abnormal position, intravenous Pitocin may be a valuable addition to the treatment. If given in large doses without indication or to the patient who has a contracted pelvis or an abnormal fetal presentation it will remain as lethal as it always has been. If used in inert labor it must be continued at a reduced rate after the contractions improve because when it is discontinued completely the uterine activity reverts to its abnormal state.

The choice of the time at and the method by which labor is terminated may make the difference between success and failure. We allow labor to continue as long as there is definite evidence of progress and as long as the mother and the fetus are in good condition. This means that almost constant observation is necessary to detect the earliest sign of unfavorable change. If by intelligent expectancy a simple outlet forceps delivery can replace a midforceps extraction, the incidence of maternal injury, hemorrhage, and infection can all be reduced and fewer infants will be sacrificed, but stubborn insistence on such a termination may be productive of disastrous results. Delivery must be considered whenever progress stops, although cessation of progress is not an indication for immediate emptying of the uterus, but more often means that a period of rest and hydration is in order; if after such a rest period labor remains at a standstill, it should be terminated.

If delivery is thought to be necessary before the cervix is completely dilated one has the choice of cesarean section or incision of the cervix and vaginal delivery. The decision is of utmost importance and depends much less upon the cervix than upon the evaluation of how difficult delivery from below will be. Since most patients whose labor is prolonged are primigravidas and since the size of the baby cannot be determined accurately, a difficult midforceps extraction may result in extensive injury to mother and infant, but if vaginal delivery can be accomplished safely it is preferable. If the presenting part is above station plus 1 in the primigravida or if there is any question as to whether or not engagement has occurred, cesarean section may be preferable to delivery from below. On the other hand, if the biparietal diameter is through the inlet and the presenting part below plus 1 and if there is no marked disproportion, delivery from below is usually feasible.

If vaginal delivery becomes necessary during the first stage one must before extraction enlarge the cervical opening. Manual "dilatation" almost always produces lacerations which cannot be controlled. Carefully placed

cervical incisions, if of adequate length, will provide sufficient room for delivery without injury; bleeding is usually minimal. If the operation is done before there is extensive cervical edema and if the cut edges are carefully approximated with interrupted sutures of chromic 00 catgut, healing usually is excellent. The difficulty arises not with making the incisions but in the delivery which may be a midforceps extraction in the face of unrecognized disproportion, but if the patients are properly selected trauma can be kept at a minimum. It is to be emphasized that cervical incisions are rarely indicated because of "cervical dystocia." The authors' conception of cervical dystocia is of a cervix made so abnormal by scarring or fibrosis that it fails to dilate with normal uterine contractions. The patients in whom we most frequently find incisions to be necessary are of the type in whom the uterine contractions are at fault; the cervix is soft and pliable at the onset but may hang like a cuff and eventually become edematous as though the uterine dyskinesia prevented its normal retraction around the presenting part.

The place of cesarean section in the treatment of prolonged labor is not well defined. We have hesitated to deliver these patients abdominally because of the increased risk from infection and because in most cases the subsequent labors are short and pregnancy and delivery are made far more hazardous if there is a uterine scar. On the other hand it is likely that in the past too few patients in prolonged labor have been delivered by the suprapubic route. Cephalopelvic disproportion has been overlooked because the size of the infant was misjudged and a traumatizing delivery has been carried out, or, at the time delivery became necessary, it was felt that the risk of a difficult vaginal delivery was less for the mother than cesarean section. By this choice many infants who otherwise might have been born alive and healthy were sacrificed. In most instances a decision as to whether or not vaginal delivery is possible can be made within the first 24 to 30 hours of labor when abdominal delivery is relatively safe. We are not able to say what percentage of patients should be delivered abdominally but the end results of the management of these patients indicate that no radical change is necessary. We believe, however, that a slight increase in incidence primarily in the interests of the infant may be warranted.

Labor with breech position may be slowed because of failure of the breech to descend through the pelvis, usually the result of splinting of the body by the extended legs and eventually requiring decomposition and extraction. Labor may be unnecessarily prolonged by failure to recognize a completely dilated but unretracted cervix hanging loosely about the presenting part which, unless carefully evaluated by vaginal examination, may be mistaken for incomplete dilatation. Extraction after a maximum of 1 to 2 hours in the second stage without descent is indicated and might prevent fetal deaths such as that of our breech infant who died of pneumonia after a 43-hour labor.

Postpartum hemorrhage should be anticipated and preparation for its management must be made. The choice of the time at which delivery is carried out may be important in prevention. For instance, a period during which the uterine activity is at a minimum is unsafe because we must rely upon an active uterus to control bleeding, and if it is not contracting during labor there is no reason to expect it to contract efficiently after it is empty. Fluids and equipment for intravenous therapy should be available in each delivery room and in addition properly matched blood should be available for immediate use in these patients should the blood loss exceed a safe amount.

The selection of a proper anesthetic for delivery is of utmost importance. For vaginal delivery, particularly if difficulty is anticipated, complete relaxation of voluntary muscles is desirable, but with inhalation anesthetic agents

this can be achieved only by compromising uterine contraction which may increase blood loss. The accompanying anoxia may also add to the risk of the fetus. The intraspinal injection of 5 mg. of Pontocaine in 10 per cent dextrose by the saddle-block technique provides excellent anesthesia and muscular paralysis without affecting uterine activity and without interfering with fetal oxygenation unless there occurs a fall in maternal blood pressure, and it is used in most patients as terminal anesthesia for delivery. An almost constant check on maternal blood pressure and fetal heart rate is kept after the anesthetic is given and oxygen is administered to the mother at the least suggestion of a change. For breech extraction or version, complete uterine paralysis is necessary and for this purpose regional techniques are inadequate since they do not relax the uterus. The most suitable agents are drop ether or chloroform carried to a point at which the utreine activity is completely abolished. The incidence of postpartum hemorrhage can be reduced by stopping the anesthetic after version or decomposition of the breech, with none given during the extraction.

The emphasis during the immediate postpartum period should be upon restoring the patient to normal as rapidly as possible. Excessive blood loss at delivery must be replaced by transfusion, dehydration corrected by adequate amounts of intravenous glucose, and adequate rest secured by the use of analgesic and hypotonic drugs. Careful observation for the first 24 hours post partum for adequacy of urinary output, for shock, and for postpartum hemorrhage from uterine atonicity or vaginal injuries is important. Penicillin by injection and sulfadiazine by mouth should be maintained until the patient is afebrile or for 48 hours if she has no fever. Ambulation may be encouraged as soon as the patient is rested, usually on the first postpartum day, as activity and walking will increase uterine drainage and perhaps reduce the incidence of endometritis.

Care of the infant begins during labor and is in part accomplished by adequate treatment of the mother. For instance penicillin and sulfadiazine traverse the placental barrier, producing an adequate therapeutic blood level in the infant, and aid in combating infection which may gain admittance through aspiration of uterine contents or through the circulation. The prevention of dehydration by the administration of sufficient amounts of fluid reduces hemoconcentration and thus provides more adequate oxygenation of the fetus. Administration of oxygen to the mother, if there is evidence of intrauterine fetal distress, may be followed by a return of the fetal heart to a normal rhythm and may in some instances prevent intrauterine death. Selection of the proper time and method for the termination of pregnancy and the proper anesthetic will also reduce fetal damage.

The fact that the baby is sick and shocked is frequently not recognized and the immediate postdelivery care often tends to exaggerate the condition. Gentle handling and the use of a hot crib in which the infant is placed with his head lowered about 15 degrees will aid in his recovery. If there is any difficulty in initiating respiration or if there is evidence of obstruction of the respiratory tree, removal of the secretions and gentle inflation of the lungs through a tracheal catheter aid in infant survival. The administration of oxygen to these infants almost always is indicated, particularly if there has been some delay in breathing. Aftercare in the premature nursery, where oxygen and a source of heat are continued until the infant seems perfectly normal, will increase the survival rate. The antibiotic and chemotherapy started during labor is continued until there is no longer any evidence of its necessity and the babies are checked frequently by the pediatrician for evidence of pneumonitis or intracranial damage.

Conclusions

The increased maternal and fetal morbidity associated with labor of over 24 hours' duration is preventable both by measures directed toward the prevention of abnormal labor and the support of the mother and her infant while it lasts. A definite program for management of patients in prolonged labor, aimed at protecting them from infection, injury, and blood loss, should improve results. Prompt termination of pregnancy by the safest method when progress ceases and cannot be re-established will aid in reducing fetal loss and maternal injury.

References

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Discussion

DR. CARL BACHMAN.—Anyone who is familiar with this vexatious problem must acknowledge that Dr. Willson's and Dr. Alesbury's results have been good. Such results could hardly have been attained without the exercise of constant and intelligent vigilance in the management of these difficult labors. Moreover, the results could hardly have been bettered by any less conservative plan of management without making many mothers obstetrical cripples in future pregnancies.

One could wish that there were available to us in these unsatisfactory labors a plan of management less trying for our patients and ourselves than watchful expectancy. The development of such a plan, however, must await the results of further research in the field of uterine motility. In this connection, the value of clinical studies of the kind reported this evening should not be overlooked. Such studies emphasize certain features that would bear further investigation among the patients who experience prolonged labor. Thus, it is of interest that many such patients are primigravidas, and that few of them experience unsatisfactory labors in subsequent pregnancies. It is also of interest that many of them are either above normal weight at the outset of their pregnancies, or gain weight excessively during them. The principal mechanical difficulty noted in their prolonged labors, as the essayists have pointed out, does not appear to be rigidity of the cervix, but an abnormal pattern of uterine contraction. All these considerations suggest that it might be useful to investigate the personalities of these women, with a view to determining whether significant factors could be detected that would lend themselves to correction prior to the onset of labor.

PARAVERTEBRAL LUMBAR SYMPATHETIC BLOCK IN LABOR*

A Report on 500 Deliveries by a Fractional Procedure Producing Continuous Conduction Anesthesia

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THE most momentous yet the most perilous day of all human life is the day of the escape from uterine environment in the process of labor to the establishment of an independent extrauterine existence.

To what extent has the employment of anesthetic, analgesic, or amnesic agents contributed toward the hazards of birth? What is the margin of safety to child and mother which each method may offer? Is the mechanism or physiology of labor unfavorably or favorably influenced by the individual procedure? It is against this background that efficiency in pain relief in labor must be judged. Pain relief is probably the most extensively discussed and most controversial problem in modern obstetrics.

Since the advent some 100 years ago of the introduction and clinical application in surgery and obstetrics of the volatile and gaseous agents, namely, of ether by Long in 1842, by Morton in 1846, of nitrous oxide by Wells in 1846, of chloroform by Simpson in 1848, women in ever-increasing numbers at their actual delivery have been afforded relief from the resultant pain at this phase of labor. However, to accomplish these desirable results, when the above-mentioned or similarly acting agents are used, it is done at the expense of patient's consciousness, implying a more or less complete submergence of all the cerebral faculties.

At the turn of the present century the usage of morphine, and a short time later of scopolamine, was introduced for their analgesic and/or amnesic action covering the extended hours consumed in labor. The combined application of these two drugs was popularized in 1914 and known as "twilight sleep." The various agents and methods employed since then to accomplish these results are legion. Many and divergent chemical agents have been introduced and have been employed for their anesthetic, analgesic, and amnesic effect in the course of parturition. Their usage was largely brought about by popular demand to have the process of labor conducted free from pain and memory of events.

The relief of pain by the encephalic approach, through which all such medicaments act, is attempted obliteration of pain at its site of interpretation

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at the sensory centers of the brain and at the higher mental levels. It often implies ablation of the functions of orientation and reasoning. Morphine and scopolamine have a narcotic action on the cortex, the latter acting by depressing mentation. The various barbiturates produce a hypnotic effect on the thalamus. Hyperexcitability may be noted at times, as well as evidence of deleterious afferent impulses being received from the uterus, giving rise to restlessness.

It is the fetus or the newborn child, however, who must bear the major brunt of the pharmacological and toxicological action of the group of drugs which are under consideration. They all pass rapidly by the transplacental route to the fetal circulation, and are retained for a number of hours before detoxification and elimination. In general, it might be stated that the possible degree of toxicity to the fetus is in direct proportion to total dosage of drug or drugs employed, with the time of administration to the time of delivery taken into consideration. The potential danger to the child in the employment of these chemicals becomes ever more clearly understood since such studies as those of Rosenfeld and Snyder[1] have been made of intrauterine respirations, when considered with the effects of anoxemia on the vital centers.

Autopsy findings made by several investigators (notably Adair and Potter, D'Esopo and Marchetti, Labate, Henderson, and Sturrock[2]) rank pulmonary pathology as the primary cause of fetal as well as neonatal deaths. The lesions of massive hemorrhage, partial or nonexpansion of the lungs, and pneumonia, together with the functional diagnosis of asphyxia and atelectasis, are the prevalent conditions. The extreme sensitivity of the fetal respiratory system to narcosis, producing a state of depression (common to all of the drugs employed to produce analgesia, amnesia, or anesthesia which act by way of the encephalic approach) has been a finding of first magnitude. Respiratory movements, it has been observed, may be abolished in the fetus at a level of analgesia which does not impair maternal respiration. It is necessary that extreme caution in the usage of these agents in the premature should be exercised. The fetus who is already under the burden of asphyxia from a pre-existing cause may be particularly vulnerable to any additional load.

The attempt to secure complete relief of pain, as well as the obliteration of all memory of events in the ordeal of labor, too often results in a marked summation of the depressive toxicological effects to the fetus produced from the several agents used. To this damage are added additional ones to the child, from the depressing effects on maternal respiration and the production of resulting anoxemia from the general inhalation anesthetic agents used in the obstetrical operative procedures. The well-known sequelae of toxicity as well as those from asphyxia serve in many cases to emphasize the tragic evidence of the toxic and depressive action of these drugs. Therefore, in the employment of these agents in labor, a compromise between the needs of the mother and those of the infant should be considered.

Various studies have been made demonstrating and emphasizing the possible inhibitory effect upon the motor activity of the uterus in labor, when excessive dosage of the drugs under question has been administered. Under such circumstances the efficiency of the physiological mechanism of labor, as well as the action of the uterine structures to control blood loss after delivery, may thereby be interfered with detrimentally. (To mention but a few who have lent support to these statements may be listed: Clifford and Irving; Sheldon; Rovenstine; Rosenfeld and Snyder; Darke; Kosmak; Eastman; Stander; and many others.[3])

Anatomic Approach to the Control of Pain

Regional block anesthesia utilizes local anesthetics to prevent painful impulses from reaching the cortex. Under such procedure the patient's cerebration is unmodified. The general state of the patient is not under the detrimental influence of anesthetic or amnesic action from drugs. What looms still more important, however, is that no depressive or anesthetic action is produced in the fetus or newborn child from drug sensitivity or toxicity.

Bilateral Paravertebral Lumbar Sympathetic Block

This procedure was first suggested and performed by Aburel[5] in 1930 to produce a complete anesthetic effect from pain in labor. Cleland in 1933 reported its use in five cases in which pain due to uterine contractions was abolished. de Bellefkoid in 1943 found it to be regularly effective in relieving the pain of the first stage. Shumacker, Manahan, and Hellman in 1943 employed the procedure in 27 cases. Jarvis in 1944 studied 70 patients in whom he observed complete relief of pain. Snoeck and Pirson, in 1947, reported on 215 patients in whom they observed entire freedom from pain. (Additional reports come from Rottinghuis and Proost; Geisendorf; Pigeaud; and Leriche.)

The present study is one in which the procedure of bilateral lumbar sympathetic block was performed upon 500 patients in labor.

It introduces a simple efficient method of obtaining continuous conduction anesthesia by the employment of fractional dosages of 1 per cent procaine solution with reinjections as needed throughout labor. The solution is deposited bilaterally in the area at which the lumbar sympathetic chain descends at the region of the first lumbar vertebral body, located well anteriorly along its lateral anterior surface. The patient is subjected to the insertion of but one needle on each side. These are promptly removed following the original injection of the anesthetic solution, but not until special fine plastic catheters are placed through the needle lumen. These tubings serve to carry the anesthetic solution to the selected anatomical area as often as may be subsequently indicated. It is thus possible for the patient to receive continuous conduction anesthesia from the time of the earlier phases of labor, carried through to its completion at birth. By this procedure a direct approach is afforded to reach a limited part of the autonomic nervous system, namely, a segment of the lumbar sympathetic chain and ganglia at the first lumbar vertebra, containing afferent and efferent fibers to the uterus, cervix, and vagina. A clearer understanding of the desired aim of this procedure may be gained by presenting a short review of the neurophysiology concerned in active labor. The uterus, cervix, vagina, and supporting structures have a dual innervation from the autonomic nervous system, namely, that from the sympathetics and parasympathetics. In the process of labor they become activated, and demonstrate a balanced opposition to each other in their controlling mechanism. The parasympathetic efferent impulses activate power to the longitudinal musculature through which the uterus attempts to evacuate its contents. In so doing it meets the resistance of the contracting circular muscular structures which are innervated through the sympathetic efferent fibers. A sensation of pain results from stimuli activated by the resultant distention, tension, and pulling to which these latter structures are subjected during the continued progress of labor. These afferent impulses are conducted through the sympathetics. These are conclusions reached by a large group of investigative authorities: White and Smithwick; Kuntz; and Reynolds.[6]

The subjective as well as the objective findings following the proper and accurate introduction and deposition of the anesthetic solution furnish positive and conclusive evidence of immediate therapeutic response to the blocking mechanism involved in this procedure. The patient, in full possession of her faculties, is no longer the recipient of painful sensations from the uterus and cervix; the blocking action is prompt. Should a labor contraction occur after injection in one side, right or left, has been completed, but before the opposite side has been treated, the patient will be cognizant of pain only on the uninjected side. By abdominal inspection and palpatation one observes clinical evidence of increased motility in the functioning power of the uterine body at the time of the labor contraction following the administration of the block. Tocographic readings have been studied. A comparison of rectal examinations performed before and again after the execution of the block reveals in most instances a most favorable change in the structural consistency of the cervix, as evidenced by its thinning and softness as well as its dilatation. The results are impressive, at times dramatically so. However, there are instances when this expected response does not occur. In such patients the findings observed to account for lack of effect on these lower structures may be explained by the lack of a dependent fetal circumference against this area, so as to maintain the gain achieved. However, in this latter group subsequent fractional injections may act to give the favorable results previously mentioned. One also usually observes an acceleration of the movement involved in the mechanism of labor, by which the labor is materially shortened. Rotation of the presenting part has proved to be unimpaired. The termination of labor by a spontaneous delivery or by elective perineal forceps should be expected unless indications exist independent of, and unrelated to, the paravertebral sympathetic lumbar block.

The anesthetic drug is deposited in a defined anatomical area and is limited neurologically to bathing the lumbar sympathetic chain at a particular segment. It avoids anesthetic contact with either the spinal somatic nerves, the spinal canal, the epidural or subdural or vertebral foramina areas. Contrary to other regional conduction methods used in obstetrics, in which pathways containing mixed nerve structures are bathed by the cocaine derivatives, as in all epidural or subarachnoid methods, its action is limited to the sympathetics. No evidence has been found following its employment of skin anesthesias, motor weaknesses, or parasthesias. The muscular contractions of the abdominal muscles in the second stage of labor are not impaired.

Inasmuch as the nerve innervation of the lower parturient canal, comprising the pelvic floor, perineal body, and structures about the introitus, is derived through the somatic nerves, namely, the pudendal and ilio-inguinal nerves, the sympathetic nerve block will not be effective in accomplishing a blocking of painful stimuli from these areas during the final phases of labor. A bilateral pudendal nerve block, therefore, is utilized to produce regional anesthesia at these levels. The timing of the administration of the pudendal block, however, is at variance with the usual custom in obstetrics. It is given at an earlier time, namely, in a multipara at about four-finger cervical dilatation, in a nullipara after the onset of the second stage. The usual objection of producing an impairment of the expulsive efforts when given too early is invalid when the patient receives a lumbar sympathetic block, as in the latter instance the so-called voluntary action of the abdominal forces is well maintained. Following the pudendal block the patient is relieved of the sensation of distention and bulging against the structures of this part of her anatomy.

The patient receiving a paravertebral sympathetic block, by continuous conduction anesthesia with employment of a fractional method, is observed as a

mentally alert, interested, appreciative, comfortable, and cooperative patient. She willingly uses her expulsive efforts in the second stage of labor. As none of the usual analgesic, amnesic, or anesthetic drugs has been employed, her cerebration is clear. She fully enjoys what is and should rightfully be the most thrilling experience of her life. She is a living part of it. She may lie in comfort in any position desired. She may rest or sleep or be entertained. She may imbibe freely of fluids, as general anesthesia will not be employed unless an obstetrical complication might indicate it. The obstetrician is afforded the opportunity of a well-controlled delivery. With this method the newborn child may be expected to breathe deeply and cry immediately at birth, having a good pink color, and possessing a good muscular tone. The respiratory tract usually is found free from aspirated material. These will be the observed findings, unless some obstetrical dystocia factor may introduce complications. The procurement of a refreshing sleep after the completion of labor is advisable.

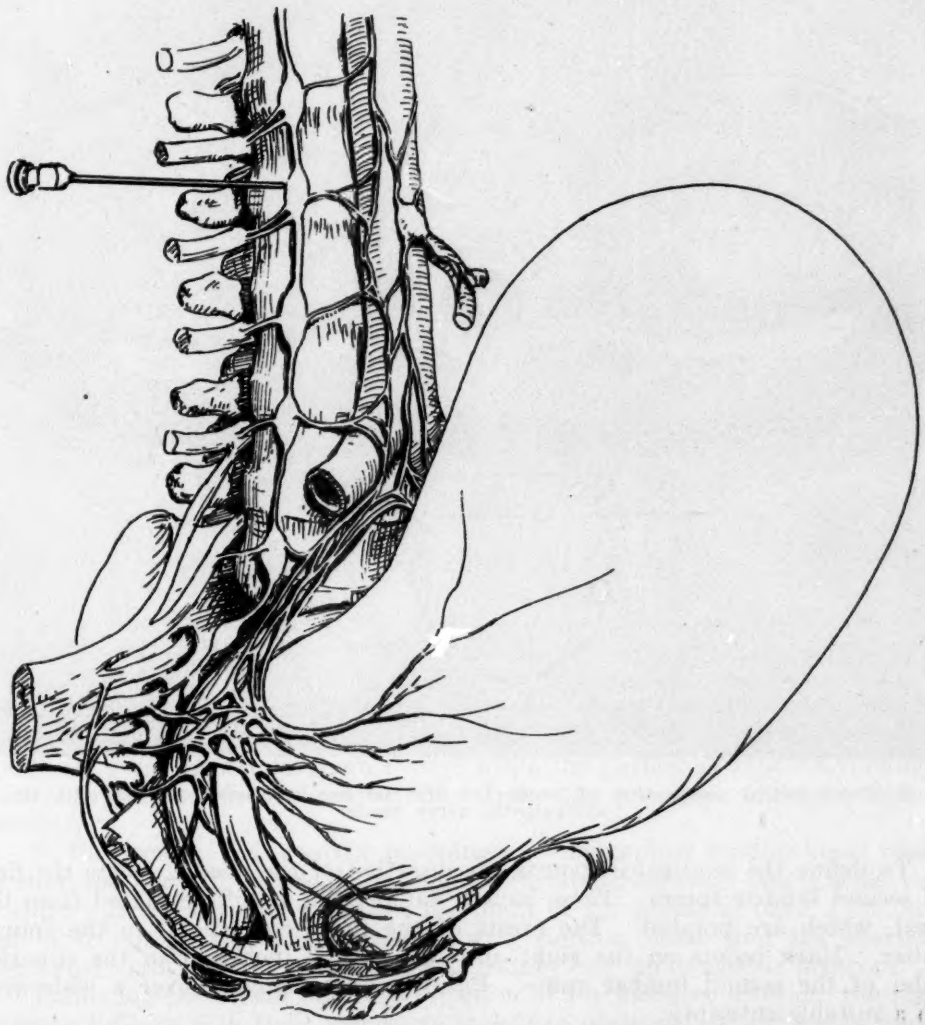

Fig. 1.—Nerve supply of uterus and birth canal. Approach of needle from posterior surface at first lumbar to reach the vicinity of lumbar sympathetic chain running along ventral lateral surface of body of first lumbar vertebra.

Technique

Nembutal, 1½ grains or 0.1 Gm., is given about one-half hour before starting the procedure. The purpose is to counteract the possible stimulating effect of cocaine derivatives.

Administration is begun at such time as contractions are sufficiently strong to produce progressive cervical dilatation, of one or two fingers.

The patient is placed in the labor or delivery room, a precaution, as labor may advance rapidly after administration.

The posture for the initial injection is sitting up with the feet and legs over the side of the bed, the body arched forward, the hands in front of the patient on the bed.

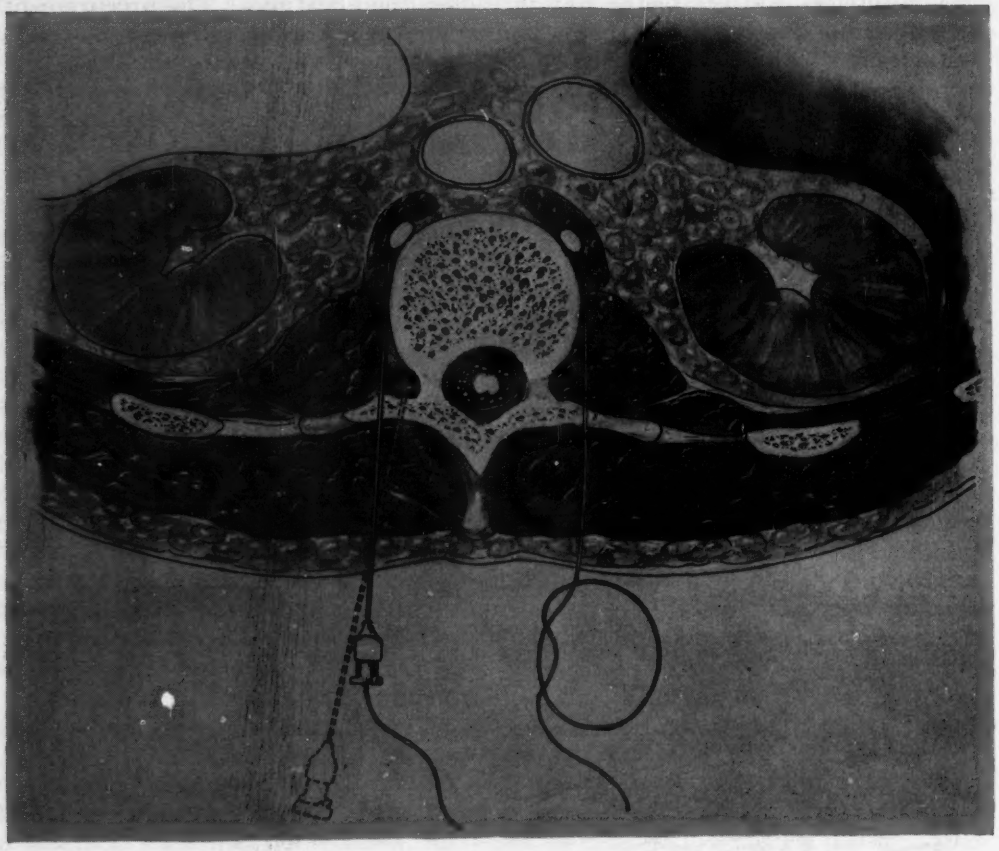

Fig. 2.—Dorsoventral penetration of needle at first lumbar. Catheter left in situ, tip at sympathetic nerve chain.

To define the anatomical points for insertion of the needle, locate the first and second lumbar spines. These have a flat plateau as differentiated from the dorsal, which are pointed. The crests of the ilium correspond to the fourth lumbar. Mark points on the right and left side, 2 inches from the superior border of the second lumbar spine. Paint the skin surface over a wide area with a suitable antiseptic.

Special needles with stylets locked are inserted. Skin wheals are made with 1 per cent procaine solution on each side directly above the marks. A 4¼ inch special needle, held properly in the grasp of the fingers, is held at an angle of

15 or 20 degrees toward the median line as it penetrates into the body. At a distance of about 5 cm., the periosteum of either the transverse process or the lateral surface of the vertebral body of the first lumbar vertebra is reached. The needle is now pulled out 1 cm. or so, and it is angulated at only 5 or 10 degrees; as it advances forward the point gently hits against the vertebral body. The forward ventral advance continues usually a distance of 4 or 5 cm. after the original contact with the periosteum. In the average individual the needle is now in about 3¾ to 4 inches from the skin.

The location of the sympathetic chain is at the first lumbar vertebra. This runs along the lateral surface of the vertebral body but close to its very anterior part. It is approximately 4 cm. anterior to the foramina.

The needle on the opposite side is similarly placed.

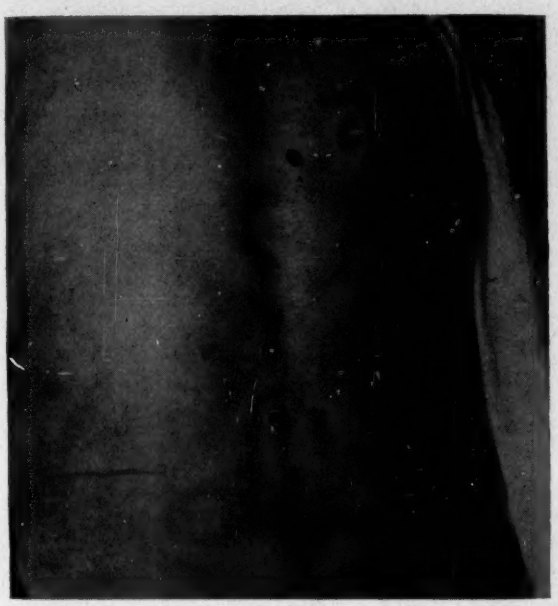

Fig. 3.—Anatomical markings. Lumbar spines, first through fourth. Two inches to right and left of second lumbar spine at its superior border.

As a precaution, the stylet of needle is unlocked and removed. Suction is made with a Luer Lok syringe (which should be empty of solution); the needle is then turned and suction repeated. Make sure the syringe is locked. If the tap is definitely a dry one, 25 c.c. of 1 per cent procaine hydrochloride solution are injected, the procedure being used bilaterally. The first 5 c.c. of solution should be given slowly and cautiously, while the patient is kept conversing, so that any possible deleterious reaction from the procaine might be detected promptly.

In the event of a wet tap or pumping of cerebrospinal fluid or blood passing through the bore of the needle, it would indicate penetration into a blood vessel or dura. In such event, withdraw the point of the needle at once, 1 cm. or so, and clear out the syringe. Proceed with caution, correcting the previously mentioned error. The syringe being an empty one, no danger is involved.

Following the initial bilateral injection of the procaine solution, the plastic catheter tubings with their respective stylets in place—after a check is made to see that the end of the catheter is ¼ inch or so beyond the stylet tip—are advanced through the lumen of the placed needles. The tips of the catheters now lie in approximation to the lumbar sympathetic chain.

The needles are removed together with the catheter stylets. The catheter is left exactly as inserted. Hold on to the catheter firmly while the needle is being withdrawn, so as not to cause any displacement. When the end of the needle reaches just beyond the skin edge, the catheter is held at the skin while the needle is withdrawn.

The part of the catheter lying outside the body is circled and looped around itself. Sterile dressings are applied, and held firmly in place by strips of adhesive.

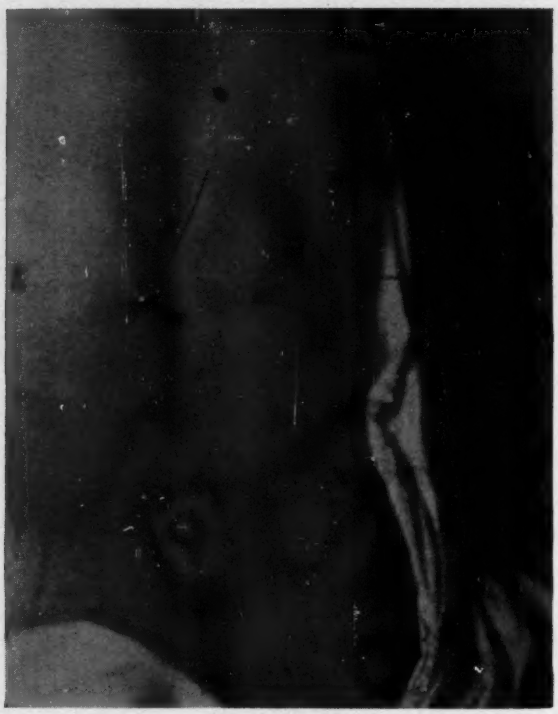

Fig. 4.—Special Becton, Dickinson plastic tubings, 10¼ inches long, with steel stylet wires, 10 inches long, in position before withdrawal of Reich needles.

Reinjections of 25 c.c. of 1 per cent procaine, bilaterally are made through the tubing under sterile precautions. The timing of the reinjections depends upon the duration of the anesthetic effect. The intervals vary from 1 to 4 hours. Should the course of labor advance to the point where it might be deemed advisable to have the patient removed to the delivery room, a reinjection would be advisable so as to assure effective action for the remainder of her labor. The procedure of reinjection may be performed with the patient either in a sitting position or turned to one side. A 23 or 24 gauge Luer Lok needle is carefully placed in the lumen of the catheter and with a Luer syringe injections are made bilaterally.

The catheters are removed after completion of delivery. The patient is now given appropriate medication for rest and sleep.

Caution should always be observed when the cocaine group of drugs is used for the detection and proper treatment of drug idiosyncrasy or toxicity. Their occurrence is infrequent. However, the employment of this particular procedure, with the use of precautions to avoid the injection of the drug into the vascular or subarachnoid or epidural areas, does not possess the potential hazards produced as a result of wide dissemination of the drug to vulnerable re-

gions. The cocaine derivatives are metabolized within ten minutes, so that toxicological manifestations, in the rare instances where they occur, will be at that time.

In the present series of 500 patients, pulse and blood pressure readings taken before and repeated ten minutes after the injections revealed the following:

The diastolic pressure dropped 20 or more points in 12 per cent.

The systolic pressure dropped 20 or more points in 25.6 per cent.

The heart rate changed 20 or more beats in 40 per cent, increasing in 32 per cent, decreasing in 8 per cent.

These changes were transitory, and the blood pressure and heart rate returned to the original readings within fifteen minutes. Occasionally one observes the patient showing evidence of some giddiness, or disorientation, or some pallor, nausea, or tremors, but for only a very short time. Two patients whose blood pressure dropped materially were given 50 mg. intramuscularly of ephedrine sulfate, and responded promptly and favorably. In one patient whose Wassermann test showed a 4 plus reaction, a single tonic and clonic convulsive seizure occurred 8 to 10 minutes after the administration of the block. She was given Sodium Amytal, 3¾ grains intravenously. A spontaneous delivery of a living child occurred 28 minutes afterward.

Results

This study presents the results of paravertebral sympathetic lumbar block, with the employment of the fractional technique, in 500 patients in labor, comprising both those on the public service and among my private patients, with 1 per cent procaine solution used for the blocks. The relief of pain is accomplished in a positive and conclusive manner. The action is immediate and completely effective. The exception to this rule would indicate that the solution was injected at a faulty site, and for this reason it failed to render optimum results. Moreover, if the reinjections are not administered at the necessary intervals, according to the needs of the patient, continuous conduction anesthesia will be interrupted. The patient, following the injection of the block anesthesia, may at times experience a sensation of distention in the pelvic region during a uterine contraction. Also at times a dragging sensation suprapubically is experienced. This occurs only on occasions. At or about the time of the second stage of labor the patient is conscious of a feeling of bulging as well as of distention. Pudendal nerve block will relieve the situation.

The advantages of this procedure, other than the relief of pain, are:

A. The necessary physiological changes of labor occurring in the lower uterine segment and the cervix are distinctly favorably enhanced.

B. The mechanism of labor is advantageously influenced.

C. The forces of labor are either effectively increased or at least remain undiminished.

D. The duration of labor is materially shortened, often strikingly so.

E. The second stage is characterized by efficient power and expeditious accomplishment of the mechanism of labor.

F. The termination of labor by a spontaneous delivery or by elective perineal forceps may usually be expected.

G. The newborn infant breathes deeply and cries immediately with his delivery. He presents no evidence of anoxemia or massive aspiration of foreign material, unless some unrelated obstetrical problem has intervened.

H. The mother is cheerful and relaxed. Her faculties are unimpaired. She truly is a willing, interested participant in her own labor and in her own delivery.

TABLE I. DURATION OF LABOR AFTER ADMINISTRATION OF PARAVERTEBRAL LUMBAR SYMPATHETIC BLOCK, IN MULTIPARAS

	PRIVATE	SERVICE
Average Duration of First Stage:		
Injection at 1 finger's dilatation	1 hour, 43 min.	1 hour, 39 min.
Injection at 2 fingers' dilatation	51 min.	65 min.
Injection at 3 fingers' dilatation	5 min.	27 min.
Injection at 4 fingers' dilatation	5 min.	17 min.
Average Duration of Second Stage	20 min.	20 min.

TABLE II. DURATION OF LABOR AFTER ADMINISTRATION OF PARAVERTEBRAL LUMBAR SYMPATHETIC BLOCK, IN NULLIPARAS

	PRIVATE	SERVICE
Average Duration of First Stage:		
Injection at 1 finger's dilatation	6 hours, 27 min.	4 hours, 34 min.
Injection at 2 fingers' dilatation	2 hours, 25 min.	3 hours, 53 min.
Injection at 3 fingers' dilatation	1 hour, 57 min.	3 hours, 49 min.
Injection at 4 fingers' dilatation	25 min.	2 hours, 4 min.
Injection at rim		35 min. to delivery
Average Duration of Second Stage	52 min.	41 min.

Tables I and II show the average duration of labor after the sympathetic nerve block has been administered, according to the dilatation of the cervix found at the time of injection, in multiparas and in primiparas.

The average duration of labor among the service patients was longer as compared with that of the private group. This finding has an important bearing in bringing out certain facts regarding the efficacy of the procedure. The patients in the private group had this method used in labor as an elective procedure, instituted as early as possible according to the time of arrival of patient at the hospital. They were educated and prepared psychologically during the antepartal period for the employment of the method and its values had been explained. They were eager to have it employed during their own labors. They benefited from a procedure planned so as to afford the patient continuous anesthesia by a fractional technique of reinjections of the anesthetic solution to the very conclusion of labor.

TABLE III. TOTAL NUMBER OF PATIENTS, 500, PRIVATE AND SERVICE

	PRIVATE (%)	SERVICE (%)
Parity.—		
Nulliparas	50	69
Multiparas	50	31
Type of Delivery.—		
Spontaneous, including assisted breech	46	78.4
Low forceps elective perineal	50	18.0
Midforceps	4	2.6
Cesarean section	0	0.8
Internal podalic version	0	0.25
Complication.—		
Postpartum hemorrhage	0	0.8

Table III demonstrates the grouping of patients according to parity, the method of delivery, and the complication of postpartum hemorrhage. It is to be noted that more than two-thirds of the service patients were nulliparas. The high incidence of spontaneous deliveries becomes accordingly more significant. The tonicity of the uterus following delivery was noted to be excellent. Blood loss seems to be held to a minimal amount.

The employment of a paravertebral lumbar sympathetic block for the induction of labor, in conjunction with the use of a pituitary infusion, administered immediately after the sympathetic nerve block, is shown in Table IV. It was used in 28 patients, 20 nulliparas and 8 multiparas. In 4 of the number, pituitary infusions had previously been given to the patients without success. In the entire series of 28 patients excellent results were obtained not only in securing successful inductions, but also in completely eliminating the pain of labor, the patients developing effective forces together with rapid labors. The indications for inductions included pre-eclampsia, premature separation of the placenta, pulmonary tuberculosis, ruptured amniotic sac, infected amniotic sac. In all but one case a living infant was obtained. The one stillborn infant was shown by autopsy to have miliary tuberculosis, while the mother was known to have active bilateral pulmonary tuberculosis. The mortality is shown in Table V.

TABLE IV. DURATION OF LABOR IN 28 PATIENTS WHO HAD LABOR INDUCTIONS. PARAVERTEBRAL SYMPATHETIC BLOCK IMMEDIATELY FOLLOWED BY PITUITARY INFUSIONS

	AVERAGE DURATION OF FIRST STAGE	AVERAGE DURATION OF SECOND STAGE
In nulliparas	7 hours, 10 min.	47 min.
In multiparas	2 hours, 59 min.	31 min.

TABLE V. MORTALITY AMONG 500 PATIENTS WHO RECEIVED PARAVERTEBRAL SYMPATHETIC LUMBAR BLOCK IN LABOR

Maternal deaths	0
Stillbirths and neonatal deaths	3, or 0.6%
1. Platypelloid pelvis. First labor, stillbirth, forceps. Second labor, living child, midforceps. This labor, second stage, fetal distress, low forceps. Unusually tight cord about neck. Stillbirth. Autopsy: nonexpansion of lungs.	
2. Active pulmonary tuberculosis, bilateral amniotic sac infection, stillbirth. Autopsy: tuberculosis of spleen.	
3. Prolonged dry labor of 41 hours, nullipara. Normal spontaneous delivery, neonatal death, fifth day. Autopsy: hepatosplenomegaly.	

A low incidence of stillbirths and neonatal deaths clearly emphasizes the clinical observation of noninterference with the physiological mechanism of fetal aeration in utero, and is evidence of the absence of asphyxia with paravertebral lumbar sympathetic block. There were no maternal deaths.

Conclusions

1. The control of pain and fear in labor has brought a challenge to the obstetrical specialist. In the therapy employed to accomplish this effect, the two patients, both mother and child, should be protected against any possible deleterious action of the agent utilized. Pharmacological damage should be held to a minimum degree. Adverse results in the physiological processes and the mechanism involved in labor should be avoided. The choice of the method administered to the patient should be considered against this background.

2. The large group of drugs used for their analgesic, amnesic, anesthetic action, which owe their results to their effect on the encephalon, have all in common a depressive pharmacological action resulting in some degree of anoxemia. Pathological processes in the lungs may well be initiated on occasion, owing to a changed physiology.

3. The anatomic approach for the prevention of pain, through which procedure stimuli emanating from the uterus and parturient tract are blocked by cocaine-derivative drugs, possesses the advantage of not producing a depressive action. The epidural and subarachnoid methods distribute the drug to a wide area, thereby resulting in anesthetizing additional nerve pathways beyond those from the generative tract. Undesirable results occur in the somatic nerve distribution. The motor activity required to complete delivery is interfered with.

4. Bilateral paravertebral lumbar sympathetic block with the use of the anesthetic properties of a 1 per cent procaine solution accomplishes complete and prompt relief of the pain of labor. The anesthetic solution acts purely upon the sympathetic pathways, blocking the afferent and efferent innervation to and from the uterus, cervix, and upper vagina which are conducted through the sympathetic nervous system, and reached at the level of lumbar 1.

5. A means of obtaining continuous conduction anesthesia is introduced by special plastic catheters which remain in situ. A most practical and technically easy method is offered to conduct the patient's labor freed from painful stimuli arising from the uterus and cervix. It is commenced during its early stages and is continued to its completion at delivery by fractional reinjections. A pudendal nerve block is performed in the second stage so as to block the stimuli arising from regions innervated by somatic nerves.

6. Its comparative safety, its efficiency in promoting rapidity of the process of cervical dilatation, and of accelerating the forces as well as the mechanics of labor, in addition to leaving the patient with a clear cerebration, freed from painful stimuli, fear, and tension, and permitting the delivery of a newborn infant whose appearance is that of a well-aerated child, commend the method as a procedure of choice in the conduct of labor.

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The author also wishes to acknowledge his appreciation for the contribution of Dr. Frank Netter for his artistic schematic sketches, to Oscar Schwidetzky, Director of Research of Becton, Dickinson and Company for his technical assistance in developing the special needles and plastic tubings.

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Discussion

DR. H. I. FLOWERS.—The development of obstetrical anesthesia and analgesia has been gradual and evolutionary. From the year 1903 when Sicard gave the first caudal until today, we have been advancing by simple steps to the highly specialized, but effective methods of pain relief that we now use. It might well be that another step has been taken in the determination of a safe method of analgesia for the mother. We do not have a perfect or completely safe method of obstetrical analgesia, but we are moving forward in our attempts to develop such a method. The accomplished anesthetist and the accomplished obstetrician should not have merely one method of pain relief, but he should have many methods which are desirable, so that he may use the type which is most effective in the situation in which he finds himself. I think Dr. Reich is to be congratulated on the material which he has presented and the step he has taken in developing an entirely new method of obstetrical analgesia.

I would like to point out several factors which have occurred to me and which are related to general anesthesia. They are as follows: First, the blockage of any nerve is in direct proportion to the size of that nerve. Therefore, the sciatic nerve requires a large amount of anesthetic solution to be successfully anesthetized, whereas the lumbar sympathetic nerve is blocked by an exceedingly small amount of anesthetic agent. Would it not be just as effective to use two or three cubic centimeters of Pontocaine or Nupercaine to block the sympathetic chain and the pathways of uterine contraction (the pathways of Cleland) instead of using 25 c.c. of Procaine? Possibly the hypotension and the fall in pulse rate were due to a diffusion of a large amount of anesthetic solution from the area of the first lumbar sympathetic chain up into the thoracic sympathetic chain. The next suggestion I can think of would be to use a needle adapter to keep the plastic tube and needle sterile between injections.

If one is able to use a longer-acting anesthetic in the lumbar area in combination with a pudendal block, one may avoid the complications that occasionally occur with intradural or peridural anesthesia. However, one must never underestimate the skill required and the dangers possible with any lumbar block. Dr. Reich has outlined these and we must be cognizant of these facts.

DR. REICH (Closing).—Due consideration was given to the selection of the most desirable preparation among the cocaine group of drugs for the purposes to be accomplished in this procedure of sympathetic block during the course of labor. Procaine seemed to be the most desirable choice. It is generally accepted to be far the least toxic as compared with Metycaine, Pontocaine, or Nupercaine. Moreover an adequate amount of solution, 25 c.c., is desirable so as to permit the anesthetic solution to bathe the sympathetic chain, in the region selected for the deposition of the product. Dr. Flowers' suggestion of employing 2 c.c. of a Pontocaine solution may not, because of its concentration, reach the sympathetic chain to accomplish the desired results. The employment of fractional reinjections as may be needed for the individual case makes it less essential to utilize the longer-acting drugs. While the reactions from Procaine solutions are minor as well as very transient in their action, yet the obligation to detect them is paramount. We should be alert in detecting the rarer, more severe reactions which should respond favorably as well as immediately to proper therapy.

CONTINUOUS-DROP SUBARACHNOIDAL BLOCK WITH DILUTE PROCAINE SOLUTION FOR LABOR AND DELIVERY

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REGIONAL anesthesia has been used for some time to relieve the pains of labor and delivery. Many different methods of spinal and fractional spinal anesthesia have been used for this purpose.[1, 2, 3, 4] Regional anesthesia causes the least disturbance of maternal metabolism and it has no depressant effect on the newborn. To minimize both the local and systemic effects of any form of conduction anesthesia on the mother, a drug should be selected which combines the advantages of quick action, rapid excretion, and freedom from toxicity. For painless labor and delivery, the afferent visceral fibers from the fundus and body of the uterus, the afferent parasympathetic fibers from the cervix and upper vagina, and the somatic afferent fibers from the lower vagina, vulva, perineum, and rectum must be blocked.[5] All these sensory pathways enter the spinal cord below the tenth thoracic segment.[14] The autonomic motor innervation to the uterus leaves the cord at a higher level.

It has been shown that different concentrations of the same anesthetic agent are required to paralyze conduction in various fibers. It was found that the thin, nonmyelinated sensory fibers can be paralyzed by a more dilute solution of a local anesthetic agent than can the thicker myelinated motor fibers.[3, 15] The fact that the origins of the sensory and motor innervation of the structures involved in delivery are at different levels in the spinal cord and that the sensory nerves can be anesthetized with solutions of lower concentration than motor nerves makes possible a "differential spinal" technique.[9]

Our objective has been to utilize this principle of "differential subarachnoid block" to develop a safe method which would (a) afford early pain relief without interfering materially with the progress of labor; (b) allow the patient to assume any comfortable position; and (c) obviate the necessity of continuous observation of the level of anesthesia by the anesthetist. The recent development of a vinylite catheter that can be autoclaved repeatedly and can be introduced into the subarachnoid space through a special thin-walled 18-gauge spinal needle simplified this problem.*

Material and Method

The observations here presented were made on 52 parturients. The technique was developed on the first 22 patients; in all subsequent cases the technique to be described was used. With the exception of Demerol (50 mg. intra-

*The vinylite catheter and the special thin-walled 18-gauge spinal needle were kindly supplied by Mr. Oscar Schwidetzky of Becton, Dickinson and Company.

muscularly, every 2 hours as needed), no sedative or analgesic drugs were administered to the patients during labor and delivery.

Special Equipment:

1. Special bore 18-gauge 3 inch Quincke spinal needle.
2. Vinylite catheter (O.D. = 0.038 inches; length, 20 inches).
3. Blunted hypodermic needle, ½ inch, 23-gauge.
4. 417A Becton, Dickinson metal plug for female Luer-Lok adapter.
5. No. H/468L Becton, Dickinson adapter.
6. 250-ml. flask of normal saline with Venopak set.
7. Tunnel clamp.†
8. Stop watch.

Solutions:

1. 1-ml. ampule of 1 per cent Novocain containing 50 mg. ephedrine.
2. 8 ml. of 2.5 per cent procaine hydrochloride in normal saline.
3. 300 ml. of 0.5 per cent procaine hydrochloride in normal saline.

Procedure.—Continuous-drop spinal anesthesia was started when labor had definitely begun as indicated by the usual signs of regular, strong, painful contractions and increasing effacement with dilatation of the cervix. The patient was turned on her side, her back carefully prepared with antiseptic solution, and the skin and underlying structures at the level of the third lumbar interspace were infiltrated with 1 ml. of Novocain-ephedrine solution. A spinal tap was then made with the special 18-gauge needle and the vinylite catheter introduced 1 inch into the subarachnoid space.

While the spinal needle was being removed, care had to be taken to keep the catheter in place. It was especially important to avoid withdrawal of the catheter while the needle was still in place to prevent parts of it being shorn off on the sharp needle edge. After removal of the spinal needle, a blunt 23-gauge needle was inserted into the distal lumen of the vinylite catheter and the hub of the needle was closed with a metal plug for the female Luer-Lok adapter. The catheter was then directed transversely across the back of the patient to her side and secured in this position with one long strip of 2-inch adhesive tape. Immediately following a uterine contraction, with the patient in the sitting position, 2 ml. of 2.5 per cent procaine solution were introduced slowly from a Luer-Lok syringe. Forty-five to 60 seconds after this injection, the patient was asked to lie flat on her back. She was kept in this position until the level of hypalgesia to pin prick extended to the tenth thoracic dermatome. The patient was then elevated to a semi-recumbent position by raising the back rest to an angle of 45 degrees. An 0.5 per cent procaine solution had been prepared by dissolving 1,500 mg. of procaine hydrochloride crystals in 300 ml. of normal saline in an intravenous flask to which a Venopak was attached. The Venopak tubing was filled with procaine solution and the lumen occluded with the tunnel clamp. The hose end of the adapter was attached to the rubber sleeve of the Venopak set while the lok-end of the adapter was connected to the hub of the 23-gauge blunted needle in the distal end of the catheter. A continuous-drop subarachnoidal infusion of 0.5 per cent procaine hydrochloride was begun at the rate of 3 to 4 drops per minute. With the tunnel clamp adjusted to deliver 4 drops per minute from the reservoir flask, 20 drops measured 1 ml. if the fluid level in the flask was 40 inches above the level of the patient's back. The use of the tunnel clamp facilitated adjustment and maintenance of an even flow at this slow rate.

In an occasional patient the level of analgesia did not ascend readily to the tenth thoracic dermatome following the injection of the initial 2 ml. of 2.5 per

†Harvard Instrument Company, Dover, Massachusetts.

cent procaine solution. In such cases the patient was kept flat and 40 to 60 drops of the 0.5 per cent procaine solution were administered rapidly until the desired level was obtained. The bed rest was then elevated to 45 degrees and the infusion slowed to 4 drops per minute.

About 15 to 20 minutes after the start of the continuous subarachnoid drip, the bed rest was lowered to 15 to 20 degrees. This position seemed to be comfortable for most patients.

Maternal blood pressure and fetal heart tones were checked every 15 minutes. It was found advisable to check periodically the rate of the subarachnoidal drip. When rectal examination revealed that the cervix was fully dilated but that the presenting part had not yet descended to the perineal floor, the patient was instructed to "bear down" synchronously with the uterine contractions which she could discern by palpating the fundus of the uterus.

Before the patient was moved to the delivery table, 50 mg. of Demerol were injected intramuscularly. The continuous drip was discontinued and the hub of the needle in the distal end of the catheter was closed with the metal plug for female Luer-Lok.

Before the delivery, it was occasionally necessary to administer another 2 ml. of 2.5 per cent procaine solution, either because the patient had some pain or because perineal relaxation was incomplete. These patients were put in a slight reverse Trendelenburg position before the injection of the "delivery dose," following which the continuous drop was discontinued. On the other hand, if the pain relief and relaxation were adequate, the drip of 0.5 per cent procaine was continued until the baby had been delivered.

After delivery and repair, the patient was turned on her side, her back was arched and the catheter was removed carefully. A sterile gauze dressing was taped loosely over the puncture site.

To decrease the incidence of postspinal headaches, patients were kept flat in bed for 24 hours and 2,000 to 2,500 ml. of fluid were given orally each day for the first 3 days and Dexedrine, 5 mg., was give orally before breakfast daily for 7 days.[10] Patients who were dehydrated because of prolonged labor, diaphoresis, emesis, or moderate blood loss received 1,500 ml. 5 per cent dextrose in water, intravenously, following delivery.

Results

No difficulty was encountered in the introduction of the vinylite catheter. In one instance, however, the catheter slipped out of the subarachnoid space; subsequently, this patient was delivered with saddle-block anesthesia.

Following the initial dose, the level of skin analgesia rose readily to T_{10} in about two-thirds of our cases. In the remainder, the level had to be elevated by the rapid infusion of 40 to 60 drops of the 0.5 per cent procaine solution. When the bed rest was lowered to 15 to 20 degrees the level of skin hypalgesia rose to T_{6-7} in most cases. At the time of delivery when the patients were placed flat on the delivery table, the level of hypalgesia rose usually to T_4. Despite this, motor power of the abdominal muscles was well preserved in all patients. The muscles of the lower extremities also retained their motor power to varying degrees. Proprioceptive sensations paralleled the motor power. Of the 30 patients who were anesthetized with the finally adopted technique, 8 experienced slight transient pain in the low back or groin during labor which was relieved promptly either by laying the patient flat for 5 to 10 minutes or by rapidly administering 40 to 60 drops of the 0.5 per cent procaine solution. It has been our experience that in order to have satisfactory relief of pain during labor, the level of the skin hypalgesia should be maintained at approximately T_8. However, if the level of hypalgesia progressed above T_6, the patients sometimes became nauseated.

TABLE I. SUMMARY OF THE ANESTHETIC MANAGEMENT OF ALL CASES

	AGE IN YEARS		PRIMIPARAS		MULTIPARAS		DURATION OF LABOR		PROCAINE USED IN MG.		DELIVERY DOSE USED		POSTSPINAL CEPHALALGIA		PAIN-RELIEF RESULTS							
															EXCELLENT		GOOD		FAIR		POOR	
	RANGE	AVERAGE	NO.	%	NO.	%	HOURS RANGE	HOURS AVERAGE	RANGE	AVERAGE	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
All cases (52)	18-40	26.5	24	46	28	54	Primiparas: 5-20½ Multiparas: 2¾-63	11.0 9.1	85-1190	386	14	27	5	9.6	33	63.5	12	23	6	11.5	1	2
Last 30 cases	19-40	26.2	16	53	14	47	Primiparas: 6½-20½ Multiparas: 2¾-63	11.8 11.5	120-1190	494	6	20	3	10	24	80	6	20	0	0	0	0

Despite the fairly high level of hypalgesia, the blood pressure of the patients remained remarkably stable throughout labor. Additional vasopressor drug had to be administered to only 1 patient in this series.

Of the last 30 patients, 24 delivered without a "delivery dose." Of the 6 patients who required the injection of 2 ml. of 2.5 per cent procaine solution just preceding delivery, 4 experienced some pain, while the other 2 did not have optimal perineal relaxation. Following the administration of a "delivery dose" or after the discontinuation of the 0.5 per cent procaine drip, the residual anesthesia was adequate for both placental delivery and postdelivery repair.

Except for terminal nausea in most patients and a moderate fall in blood pressure in one patient, no maternal complications were encountered during labor and delivery. The only postdelivery complication was spinal headache, which occurred in 3 of the last 30 cases.

From the obstetrical viewpoint the following observations were noted. After the onset of analgesia, the amplitude and frequency of uterine contractions usually decreased for 10 to 20 minutes; thereafter, the initial contraction pattern was re-established. In 2 of the 30 patients, uterine contractions did not regain their original force, despite which the course of labor was not delayed perceptibly. In 13 cases, the progress of labor was slowed due to only partially effective contractions. In these cases if (1) the fetus was not more than 3 weeks premature, (2) the cervix was soft and at least 5 cm. dilated, (3) the presenting part descended to the level of the ischial spines, and (4) there was no abnormal uterine bleeding, a solution of 0.3 ml. of Pitocin in 500 ml. of 5 per cent dextrose was administered intravenously at the rate of 30 drops per minute.[11, 12, 13] This re-established the satisfactory progress of labor in each case.

As with other methods of conduction anesthesia for delivery, the patients were incapable of giving birth precipitously or of delivering unattended. Outlet forceps were used in 18 of the 30 cases while 6 patients delivered spontaneously. We noted also that the incidence of persistent malposition of the fetal head due to failure of rotation was greater than when deliveries were done under inhalation anesthesia.

The second and third stages of labor were not prolonged and the blood loss was less than that observed under general anesthesia.

None of the babies required resuscitation; all cried within 3 to 30 seconds. There was 1 fetal death following a difficult frank breech delivery of a large baby. The delivery of the aftercoming head required 8 minutes and although the baby was delivered alive, he died a short time later. In 1 case of placenta accreta, abdominal hysterectomy was performed after injection of a supplementary dose of 3 ml. of 4.5 per cent procaine through the subarachnoidal catheter; mother and baby did well.

The anesthetic management of all cases is summarized in Table I.

Comment

It is generally accepted that regional methods interfere the least with maternal metabolism and produce the least depression in the newborn. There can be no doubt that any method employed should be the least traumatic to the maternal tissues and that the agent used should have the least local and systemic toxicity. Therefore, our goal has been to use the smallest possible needle and the thinnest catheter for the establishment of the continuous subarachnoidal block. For the same reason, procaine, the least toxic of all known local anesthetic agents, was used in the lowest concentration that served the purpose. With the use of a smaller needle, the incidence of postspinal cephalalgia and the danger of a subarachnoidal fistula should be decreased.[10] Similarly, the

use of a low concentration of procaine should decrease the possibility of any residual neuropathy. It will be pointed out later that the use of the most dilute solution has additional advantages.

For painless labor and delivery, the afferent visceral fibers from the uterus, the afferent parasympathetic fibers from the upper vagina and cervix, and the somatic fibers from the lower vagina, vulva, perineum, and rectum must be blocked. All these sensory pathways enter the spinal cord below the tenth thoracic segment. The autonomic motor innervation to the uterus leaves the cord at higher levels.[14]

The initially administered 2 ml. of 2.5 per cent procaine established both profound sensory anesthesia in the cervix, vagina, vulva, rectum, and perineum and also adequate motor paralysis of the muscles of these structures. With the technique employed, using a slightly hyperbaric solution (1.014), the procaine concentration in the spinal fluid was greatest in the area of the sacral and lower lumbar nerves. The procaine concentration gradually decreased in cephalad direction. This circumstance, together with the relatively high sensitivity of sensory fibers and the low sensitivity of motor fibers toward local anesthetic agents, resulted in good sensory analgesia below the tenth dorsal segment and hypalgesia extending anywhere between the eighth and fourth dorsal segments. In contrast to this, motor activity of the lower extremities was only partially affected while that of the abdominal muscles was almost intact. The continuous drop used for maintenance of analgesia replaced the procaine as it was absorbed.

In the first 22 cases we endeavored to maintain the subarachnoidal block with 0.3 per cent and 0.4 per cent solutions. Satisfactory analgesia could be obtained in only half of the cases. Therefore, an 0.5 per cent solution was chosen for maintenance since it afforded consistent relief from pain in all cases.

As already mentioned, an increased incidence of persisting malpositions occurred with this technique. In this regard, the method is no different from other types of conduction anesthesia used for labor and delivery.[16, 17] The probable explanation of these malpositions is the fact that there is a complete loss of motor power in the muscles of the birth canal and perineum; thus, there is insufficient counterforce to the fetal vertex to effect flexion of the head and anterior rotation of the occiput during descent. Another possible contributory factor is that, since the parturient feels no pain, the stimulus for the "bearing down" reflex is absent. The decreased intensity of the uterine contractions might also influence the development of malpositions. This last factor can be overcome by the intravenous use of dilute Pitocin solutions. It must be remembered in this respect that the partially denervated uterus like all other denervated organs has an increased sensitivity to chemical stimuli. After the cervix is fully dilated, the lack of the "bearing down" reflex can be compensated for if the patient is instructed to bear down voluntarily whenever her palpating hand feels a uterine contraction.

The nausea experienced by some patients in whom the level of skin hypalgesia extended above dermatome T_6 can be explained by the preponderance of the vagi due to sympathetic paralysis. It is interesting to note that despite the fairly high level of sensory analgesia, there did not seem to be enough paralysis of the sympathetic vasopressor nerves to cause a significant fall in blood pressure.

The technique described seems to offer the following advantages: (1) Pain relief can be afforded safely and early without significant interference with labor and delivery. In some cases the catheter was inserted into the subarachnoidal space before the start of strong contractions so that the analgesia could be started without delay as soon as the contractions became painful. (2) Be-

cause of the decreasing gradient of the intensity of the subarachnoidal block in cephalad direction, the level of skin analgesia may ascend as high as T_4 without interfering significantly with labor and delivery. In one case the level of skin analgesia was allowed to ascend to the second cervical dermatome without any retardation of labor. This dilution gradient phenomenon, which is characteristic of spinal analgesia, contrasts with the situation in continuous caudal analgesia where the level of analgesia is sharply demarcated. This demarcation is due to the fact that the solution injected into the epidural space does not become diluted, since the epidural space contains no fluid. The sensory and, to a lesser extent, the motor fibers will be paralyzed with equal intensity as far up as the injected solution spreads in the epidural space. Consequently a delicate balance has to be maintained around T_{10} in order that complete pain relief be obtained without diminishing uterine motor activity. (3) In the administration of continuous caudal analgesia, the need for constant observation necessitates the presence of a highly skilled person. This is not the case with continuous drop spinal analgesia. Once the level of the initial saddle block is stabilized and the maintenance drip has been started, the administration can be supervised by an intelligent nurse who can regulate the drip at 4 drops per minute and check the maternal blood pressure. We believe that the progress of labor and the fetal heart tones should be checked by the obstetrician. (4) Another advantage of this method is that the patient may assume any comfortable position during labor. (5) The patient does not require large doses of sedatives or analgesics; thus her sensorium is not clouded by drugs and she is able to cooperate. (6) Because relatively small amounts of a low-toxic anesthetic agent are used and the absorption from the subarachnoid space is negligible,[18] there is no danger of systemic reaction to the local anesthetic drug. (7) As the site of puncture is removed further from the anus, the danger of contamination is reduced.

The disadvantages of this method are the complications common to other subarachnoidal techniques; i.e., cephalalgia, meningismus, meningitis, and permanent nerve damage.

Continuous subarachnoidal drip is contraindicated in all cases where obstetrical spinal analgesia is contraindicated. Besides these contraindications, the method is not recommended for patients with easy, almost precipitate labor or for those who come into the hospital in the terminal part of the first stage of labor. Similarly, the method is not advised for highly nervous patients who want to be asleep during their deliveries.

Summary

1. A new method of continuous-drop subarachnoidal block for labor and delivery with an 0.5 per cent procaine solution has been described.

2. By means of this "differential" technique, complete pain relief can be afforded early to parturients without significant interference with the process of labor and delivery.

3. Because the method allows a great latitude in the level of analgesia, the continuous presence of the anesthesiologist is not necessary.

4. The technique is safe. Maternal and fetal complications attributable to the method were negligible.

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SUBEPENDYMAL CEREBRAL HEMORRHAGE IN PREMATURE INFANTS, AND ITS RELATION TO VARIOUS INJURIOUS INFLUENCES AT BIRTH*

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INTRAVENTRICULAR hemorrhage is known to occur frequently in premature infants at birth. Its existence probably accounts to a large extent for the notion that premature infants are particularly liable to mechanical cerebral birth injury. On the other hand, it has been suggested that this type of hemorrhage frequently takes its origin from subependymal hemorrhage on the surface of the caudate nuclei for which various factors have been held responsible. The present analysis of a large number of cases of subependymal hemorrhage with or without rupture into the ventricle will serve to evaluate the significance of various factors in the causation of this accident which claims the lives of so many premature infants.

Observations

Fifty cases of subependymal hemorrhage with or without perforation into the ventricles were available for the present study. Their distribution among premature infants of various weight groups, as well as obstetrical data to be discussed later, is summarized in Table I. Almost all of the present cases are derived from autopsies performed at Kings County Hospital; only a few were among those contributed by various other hospitals to the Brooklyn Survey of Neonatal Pathology. This is not due to a lower incidence in these hospitals, but rather to the fact that often no adequate specimens of brain tissue were received. The incidence of subependymal hemorrhage found in all autopsies on premature infants cannot be statistically evaluated since small foci may have been overlooked before interest was centered on this point. All gross observations were confirmed by microscopic examination. In most instances of intraventricular hemorrhage of premature infants there was subependymal hemorrhage, and the point of perforation was often identified. It is impossible to be certain that in the remaining instances intraventricular hemorrhage had a different source, because it may be extremely difficult to detect an area of ruptured subependymal hemorrhage when the overlying thin layer of tissue is completely destroyed by perforation into the ventricle.

The gross appearance of subependymal hemorrhage is illustrated in Fig. 1. Several foci of hemorrhage are seen on the surface of the caudate nucleus in Fig. 1, a; the lateral ventricle contains a large blood clot. Fig. 1, b shows in addition to similar changes also a portion of the surface of the caudate nucleus which is rough and devoid of ependyma; at this point there was presumably a broad perforation of the subependymal focus of hemorrhage into the ven-

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tricle. Scattered areas of subarachnoid hemorrhage suggestive of asphyxia are seen in the same brain. The third figure in this group shows part of a coronal section with hemorrhage in both caudate nuclei. A large blood clot fills the lateral and third ventricles. Perforation of the subependymal hemorrhage shown on the right side was demonstrated. Apart from these typical changes, small foci of hemorrhage are seen in rare cases in a thin layer of undifferentiated subependymal tissue in the lateral wall of the proximal portion of the posterior horns.

TABLE I. DISTRIBUTION OF 50 CASES OF SUBEPENDYMAL CEREBRAL HEMORRHAGE, BY WEIGHT GROUPS AND BY PART PRESENTING AT BIRTH

WEIGHT GROUPS (GRAMS)	NUMBER OF CASES	WITHOUT INTRAVENTRICULAR HEMORRHAGE			WITH INTRAVENTRICULAR HEMORRHAGE		
		CEPHALIC	BREECH	UNKNOWN	CEPHALIC	BREECH	UNKNOWN
1-500	4	0	0	1	2	1	0
501-1,000	20	4	4	1	7	1	3
1001-1,500	16	2	2	3	6	1	2
1,501-2,000	8	1	2	1	3	1	0
2,001-2,500	2	0	0	0	0	0	2
Total	50	7	8	6	18	4	7

Microscopic examination (Fig. 2) reveals single or multiple areas of hemorrhage in the subependymal tissue which consists of densely accumulated, small cells with dark-staining, round nuclei. The large vessels in this area are not regularly connected with these hemorrhages; in fact, they can often be seen intact not far from one of the lesions (Fig. 2, a and b). Perforations of subependymal hemorrhage into the ventricle can often be verified on microscopic sections. A blood clot is then found extending from a break in the subependymal tissue into the lateral ventricle (Fig. 2, c and d). Owing to the short period of survival after these hemorrhages occur, there is usually no reaction of the surrounding tissue, or accumulation of macrophages.

Comment

Most of these investigators who studied the cerebral and intraventricular hemorrhages described here have come to the conclusion that these hemorrhages are not due to purely mechanical trauma at birth. Schwartz[1] and Craig[2] noticed that in many instances subependymal hemorrhage is due to capillary oozing rather than to rupture of a larger vein; this is justly held against mechanical trauma. Schwartz[1] emphasized the difference in pressure between that part of the presenting head exposed to the outer world and the rest of the body enclosed in the contracting uterus; the lower outside pressure sucks blood into part of the brain and thus causes severe congestion and hemorrhage *(Ansaugungsblutung)*. Munro and Eustis,[3] Potter and Adair,[4] and Morison[5] held that asphyxia with its concomitant congestion and capillary damage causes the subependymal as well as subarachnoid and other intracranial hemorrhages. Ruckensteiner and Zöllner,[6] Hemsath,[7] and Morison[5] were impressed with the occurrence of subependymal hemorrhages only in the undifferentiated tissue of the ventricular wall, and assumed a particular predisposition of that tissue on the basis of its structure.

The present observations give an opportunity to evaluate the role played by each of these factors in the development of subependymal and intraventricular hemorrhage. The occurrence of multiple focal hemorrhages in the subependymal tissue speaks strongly against mechanical trauma; in this respect we agree with all of the above-mentioned authors. The existence of a special predisposition of the subependymal zone of the undifferentiated tissue

is too obvious to need further proof. The type of hemorrhage under consideration is limited to the subependymal tissue not only in its distribution in a given brain, but also in its occurrence during the period of development in which undifferentiated subependymal tissue is present, i.e., in premature infants. Hemsath[7] referred to this vaguely as a "developmental factor." Ruckensteiner and Zöllner[6] incriminated thin-walled veins and soft tissue poor in fibers. The

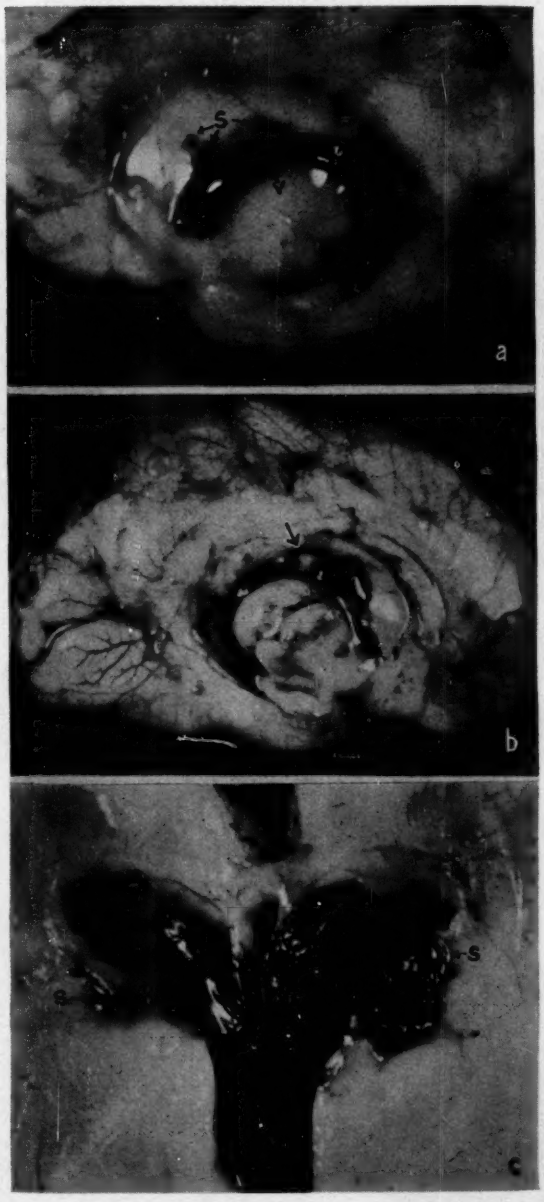

Fig. 1.—Gross appearance of subependymal hemorrhage with perforation into a lateral ventricle. a, from an infant weighing 1,080 grams, shows a large blood clot in the ventricle (v) and above it several small areas of hemorrhage on the surface of the caudate nucleus (s). In b (940-gram infant) the clot has been removed and several areas of hemorrhage are seen; one of these, at the arrow, has opened into the ventricle. c, from a 900-gram infant, shows on gross section the ventricles filled with clotted blood and subependymal hemorrhage near the surface of both caudate nuclei (s).

latter assumption is obviously correct. In order to study the thickness of vessel walls silver impregnation of lattice fibers was done on sections from 8 brains without hemorrhage, using the method of Gomori. The conditions shown in Fig. 3 are representative of all observations. Of the two veins from the same brain section, the one in the subependymal tissue has a markedly thinner wall even though its diameter is somewhat larger than that of the other vessel which is from the white matter of the adjacent hemisphere. It thus appears that the contention of Ruckensteiner and Zöllner[6] concerning the na-

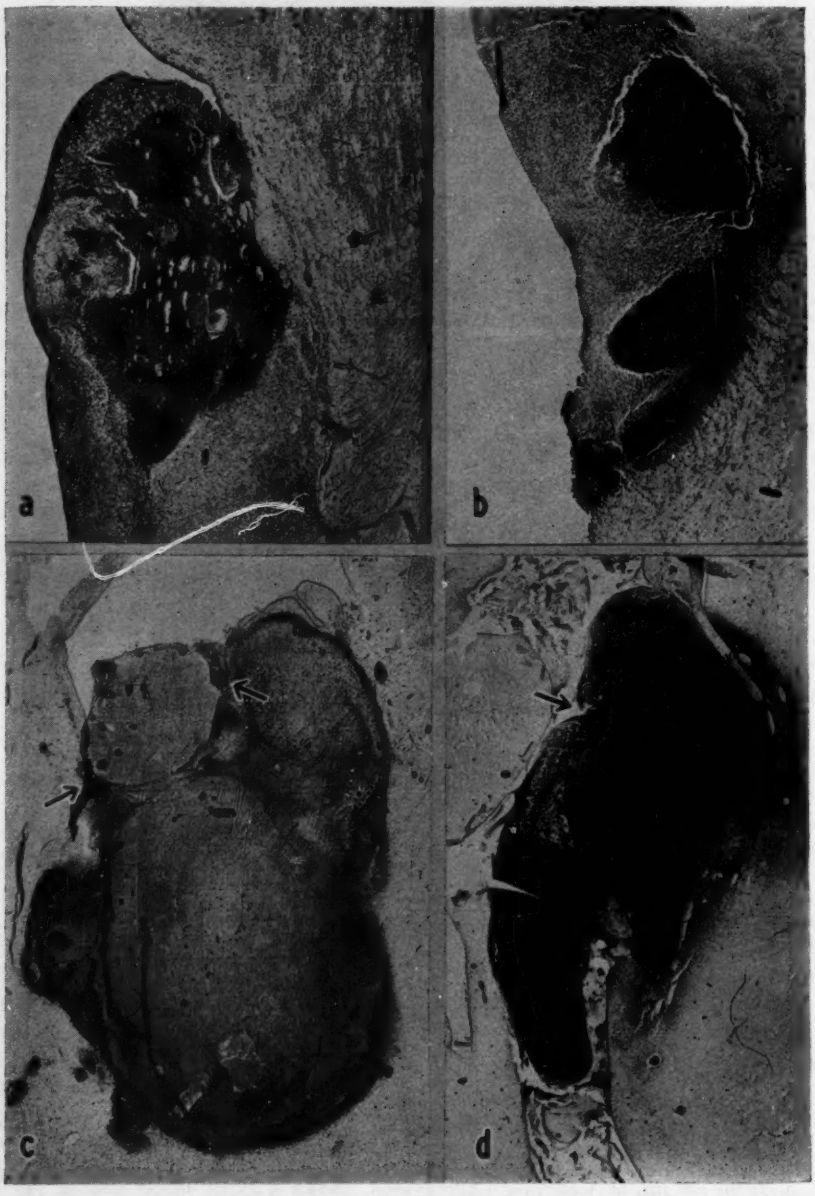

Fig. 2.—Sections showing hemorrhage in the subependymal tissue. a and b, from infants weighing 610 and 1,350 grams, respectively, show hemorrhage without perforation. In c and d from infants weighing 1,120 and 1,370 grams, perforation is indicated by arrows and part of the blood clot protrudes into the ventricle.

ture of the local predisposition to hemorrhage is correct. This explains why vessels in the subependymal tissue rupture more easily than those in other parts of the brain, when the pressure in the lumen rises.

Undifferentiated subependymal tissue occurs in smaller amounts elsewhere along the ventricular system; however, these thin layers are not as well vascularized as the one over the caudate nucleus, and they do not give rise to hemorrhage. It is possible that the close relationship to the vein of Galen via the terminal veins exposes the vessels here under consideration to back pressure of severe degrees.

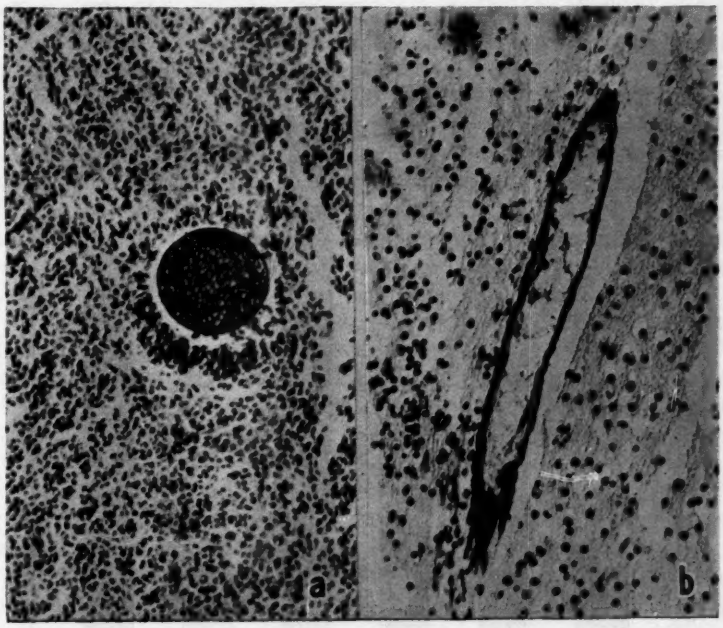

Fig. 3.—Two portions of a section from the normal brain of a premature infant showing veins (a) in the subependymal tissue and (b) in the differentiated white matter of the hemisphere for comparison of the thickness of their walls.

It now remains to examine the factors which lead to increased pressure within cerebral vessels. In order to do this, some data on the occurrence of subependymal hemorrhages with and without intraventricular hemorrhage will be presented; it will be assumed that intraventricular hemorrhage is the expression of either a severer form of subependymal hemorrhage, or a complication of it. Table I shows the incidence of intraventricular hemorrhage and, as far as is known, the presentation at birth in the present group of 50 cases of subependymal hemorrhage, arranged by weight groups. It appears that the breech presented at birth in about one-third of these infants. This shows that exposure of the presenting part to lower pressure cannot be the principal cause of subependymal hemorrhage, since that could occur only in cephalic presentation. However, some influence of this difference in pressure on the severity of the lesion is indicated by the fact that among 25 infants with cephalic presentation, 18 had intraventricular hemorrhage, whereas among 12 with breech presentation, only 4 had hemorrhage into the ventricles. A pressure difference as described by Schwartz[1] is therefore not the cause of subependymal hemorrhage as such, but may increase its severity. This is of great importance since perforation into the ventricle transforms the presumably harmless subependymal hemorrhage into a fatal lesion. It is noteworthy that while birth in

breech presentation is generally considered to be the most dangerous for premature infants, the particular lesion now under consideration tends to be less severe in this form of delivery.

If neither mechanical trauma nor a pressure difference is the principal cause of subependymal hemorrhage, another factor must be sought for. It is well known that asphyxia causes congestion of blood vessels as well as damage to capillary walls, and it appears most plausible that this is the cause of subependymal hemorrhage. It was mentioned above that previous investigators have made this suggestion, and supported it by drawing attention to oozing from small vessels which may be seen in many instances in the subependymal tissue itself as well as in focal areas in the arachnoid. These findings have been confirmed in the present material.

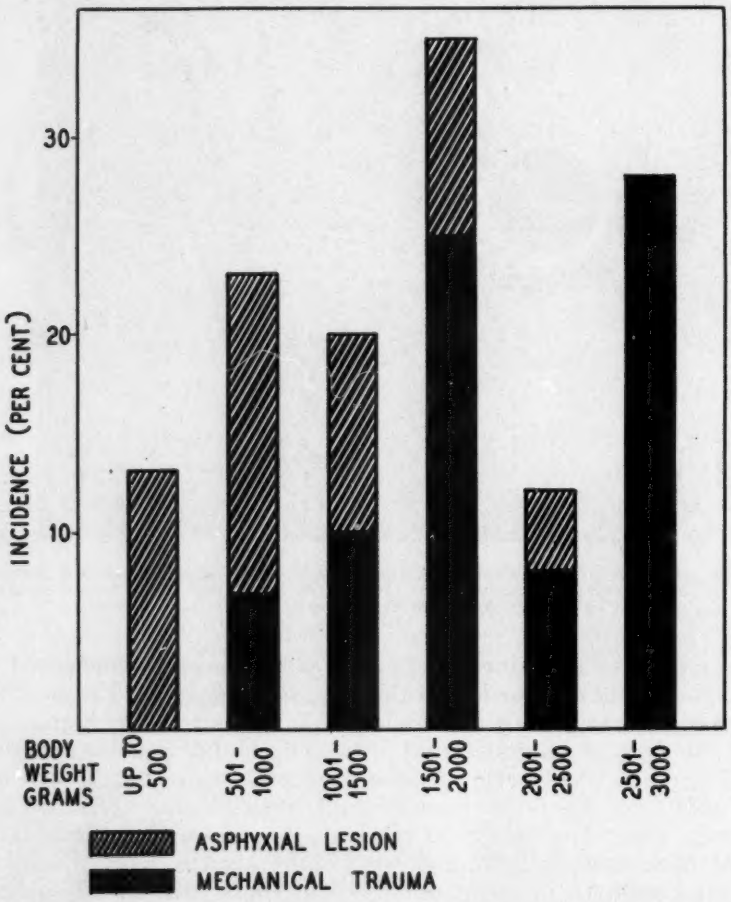

Fig. 4.—Incidence of gross hemorrhage in the brain in 349 infants. Intraventricular hemorrhage resulting from subependymal hemorrhage is considered asphyxial, all other instances are included as mechanical trauma.

These considerations establish subependymal hemorrhage as an example of the interaction of various factors in the production of a common lesion of newborn infants. The relative importance of four possible conditions may be judged as follows. A peculiar architecture is the predisposing factor, determining the localization of the lesion in the subependymal tissue. Anoxia is the primary agent; it produces focal hemorrhages in this tissue by severe congestion of the vessels and probably also capillary damage. A pressure differ-

ence between the presenting part of the head and the rest of the body, prevailing in cephalic presentation, may lead to further influx of blood into the area, and thus aggravate the hemorrhage and lead to a higher incidence of rupture into a ventricle. The fourth possible factor, namely, mechanical trauma, seems to play no role in the development of subependymal hemorrhage.

This analysis is of general significance in neonatal pathology because similar conditions may well prevail elsewhere in the body of newborn infants, even though they are not so readily analyzed. It is important to realize that not every instance of gross hemorrhage should be classified as caused by mechanical trauma without careful investigation. It is, for instance, highly probable that the great majority of instances of hemorrhage in the adrenals is similarly due to anoxia and shock rather than to trauma.[8]

A diagram presented in Fig. 4 illustrates the relative significance of anoxia and mechanical trauma in neonatal brain injury with gross hemorrhage. It is based on autopsies on a series of 349 newborn infants weighing 3,000 grams or less, including the majority of the present cases, which were analyzed elsewhere[9] for signs of asphyxia. Actually, the estimate of the role of anoxia as given in Fig. 4 is very conservative because all instances of intraventricular hemorrhage in which no foci of subependymal hemorrhage were found are listed as mechanical trauma. Many of these probably originated from subependymal foci which could not be identified because they had completely emptied into the ventricle, or from severely congested choroid plexus, both presumably due to asphyxia. Subependymal hemorrhage without perforation into a ventricle is not included. Even this conservative estimate shows that when the condition here under consideration is eliminated from the category of mechanical birth trauma, the incidence of the latter appears to be quite low in premature infants.

The present interpretation of the pathogenesis of subependymal hemorrhage further emphasizes what has been increasingly appreciated in recent years, namely, that anoxia is more important than mechanical trauma in neonatal pathology. This recalls Smith's[10] statement to the effect that mechanical obstetrics has been developed to a high degree of perfection, and that further decline of neonatal mortality should result from advances in physiological obstetrics. On the other hand, there are significant mutual relations of anoxia and trauma at birth; this has been discussed elsewhere.[8]

Summary

A group of 50 cases of subependymal cerebral hemorrhage in premature infants is analyzed; in 29 of these cases perforation of hematomas had resulted in intraventricular hemorrhage.

It is suggested that various factors incident to birth have the following significance in the pathogenesis of these lesions. Mechanical trauma plays no essential part in the causation of subependymal hemorrhage. A local predisposition is attributable to the presence of masses of undifferentiated subependymal tissue in premature infants. In these highly susceptible areas anoxia with its concomitant congestion of vessels frequently causes focal hemorrhages. The relatively low external pressure to which the presenting part is exposed may in cephalic presentation aggravate the lesions by increasing the influx of blood to the brain.

If this interpretation is accepted, a large proportion of the instances of intraventricular hemorrhage in premature infants should no longer be considered as effects of mechanical trauma.

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A CORRELATION OF HISTOLOGIC GRADE, CLINICAL STAGE, AND RADIATION RESPONSE IN CARCINOMA OF THE UTERINE CERVIX

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THE medical and sociologic importance of carcinoma of the uterine cervix cannot be overemphasized, Meigs[1] stating that it is as common as carcinoma of the breast and that 2 per cent of all women develop this disease. Recent emphasis on diagnostic procedures utilizing vaginal smears, multiple biopsies, Schiller staining, and colposcope, together with widespread cancer publicity, has brought an increased number of early cases to the gynecologist. The emphasis placed on carcinoma in situ in many teaching centers has similarly focused attention on careful observation and treatment in early cases.

The following study was carried out in an effort to see whether direct correlation existed between histologic grade, degree of radiation response, and five-year survival. This, in turn, was compared with the clinical staging in an attempt to ascertain whether these factors would aid in a more precise prognosis.

The enigma of radiation resistance and sensitivity remains unsolved. Pretreatment estimates of tissue response are, in general, unreliable and utilization of histologic gradations to gauge survival have been unsuccessful in the hands of many observers. Martzloff,[2] however, in 1923, in a careful study of 387 carcinomas of the cervix, divided the lesion histologically into spindle-cell (Grade III), transitional-cell (Grade II), adenocarcinoma and spinal- or prickle-cell (Grade I) groups, and predicted the highest degree of malignancy to exist in the spindle-cell type and the lowest degree in the spinal-cell type. It was generally accepted that the tumor with the greatest proportion of undifferentiated cells and the greatest number of mitoses was the most malignant. The law of Bergonié and Tribondeau, stating that the more embryonal the cell, the greater its susceptibility to irradiation, was tested by Norris and Kimbrough,[3] who found that tumors made up largely of embryonal cells responded to irradiation (as pertains to local healing) in 76 per cent of their cases whereas tumors with chiefly mature-cell composition showed local healing in only 51 per cent. There was, however, little difference in the survival rate. Clark and Norris[4] believed the transitional type to be the most frequent, the most malignant, the least favorable for surgery, and the most susceptible to irradiation.

Numerous interesting studies utilizing postradiation biopsy and vaginal smears have been made in an effort to set down somewhat measurable and constant criteria by which the response of the tumor to radiotherapy could be pre-

dicted. The election of surgery in those cases where minimal radioresponse is elicited would thereby be facilitated.

Pemberton[5] in 1926 studied 131 cases of which 96 had complete follow-up records, and concluded that: (1) the proportion of the three cell types was about the same in the various clinical stages and that the spindle-cell type was somewhat more malignant than the transitional or spinal types but that cell type had no bearing on the choice of treatment.

Warren and co-workers[6] analyzed 70 cases in an effort to determine the value of biopsy in prognosis of carcinoma of the cervix during and immediately after radiation. They found the histologic grading to be less significant than the clinical staging regarding survival. However, the degree of response was of importance, since 90 per cent of those patients without radiation response died, whereas all but one of the cured patients (5 years) showed a definite reaction. They noted the importance of stromal response and Warren[7] subsequently pointed out that radiosensitivity and curability were not synonymous and that tumor regression depended upon changes in the supporting stroma as well as upon those in tumor cells.

Graham[8] described 73 cases in which she studied the accuracy of the vaginal smear in the prognosis of treated cervical cancer. She calculated a prognostic accuracy of 88 per cent for the vaginal smear method, but found no correlation between the grade of tumor and the subsequent response to radiation.

Material and Methods

Three hundred fifty-four consecutive cases of carcinoma of the cervix diagnosed during the years 1941, 1942, and 1943 were reviewed. All cases in which the original biopsy was done elsewhere, or where previous irradiation treatment had been instituted were rejected. Similarly, all cases in which there were incomplete biopsy follow-ups or in which inadequate biopsies had been taken, were eliminated from the study. There remained 100 cases which were selected for detailed pathologic study.

The original diagnostic biopsy was restudied in each case together with the first follow-up biopsy taken at about the fourteenth to twenty-first day after x-ray therapy, that is, at the time of the first radium insertion. Another biopsy was taken 10 to 14 days later at the time of the second radium insertion. A third biopsy was taken either at the termination of radium therapy or 2 to 3 weeks later.

Cervical carcinomas were graded according to the method of Warren[6]: Grade I requires the presence of numerous epithelioid pearls and considerable keratinization with visible intercellular bridges and an average of less than 2 mitoses per high-power field. In Grade II pearls are rare or absent with a moderate amount of keratinization and some intercellular bridges with 2 to 4 mitotic figures per high-power field. In Grade III there are no pearls and only slight evidence of keratinization and no intercellular bridges. Mitoses number over 4 per high-power field. Marked variation in size and shape of tumor cells exists with numerous tumor giant cells.

The usual irradiation therapy program[9] consisted of: *X-ray:* 200 kv., standard apparatus, 50 cm. distance, filter of 0.5 mm. copper, an average of 5 treatments through each of 3 portals, one 15 by 15 cm. anterior and two 10 by 15 cm. posterior oblique, for an average total dose of 6,000 r, measured with

scattering, given within a period of 3 weeks. *Radium:* 2 doses of 2,000 to 3,600 mg. hr. each within 10 to 21 days of each other for a total of 4,800 to 6,000 mg. hr. The radium was given in a usual dose of 200 to 225 mg. for 24 to 30 hours, the applicators being of 1.0 mm. brass with additional screening of 1.0 mm. lead. Two 50-mg. tubes were usually placed within the cavum of the uterus and four 25-mg. tubes in a "pillbox" were applied to the surface of the cervix.

In most cases x-ray therapy was given first followed by radium in 2 doses. In those cases with profuse vaginal hemorrhage from the tumor site, radium was given first. All irradiation therapy was usually completed within a 6-week period.

Radiation response in tumor cells was graded as marked, moderate, or minimal using the criteria as shown in Table I.

The League of Nations classification of clinical staging was utilized.

Results

1. Age.—The ages of the patients varied from 25 to 77 years and the average was 49.8 years. Age could not be statistically correlated with the degree of radiation response nor with survival.

2. Stage.—Thirty-four patients were placed in Stage I, 53 in Stage II, 9 in Stage III, and 4 in Stage IV.

3. Grade.—The cervical carcinoma was histologically classified as Grade I in 4 cases, Grade II in 77 cases, Grade III in 9 cases, adenocarcinoma in 9 cases, and adenosquamous in 1 case.

4. Survival.—The over-all 5-year survival was 50 per cent. A more complete analysis is shown in the accompanying figures.

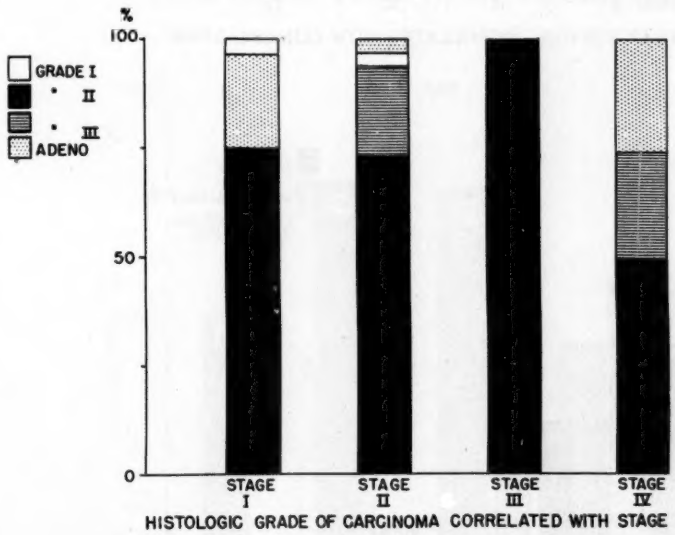

Fig. 1.

Fig. 1 correlates the various grades of carcinoma occurring in each stage. It is evident that Grade II occurred about equally in Stages I and II, made up all of Stage III, but was found in only half of Stage IV's.

Fig. 2 shows the 5-year survival in the 100 selected patients in this pathologic study divided into stages.

In an effort to compare these figures with larger representative series, Fig. 3 graphically depicts the 5-year salvage rate in the Memorial Hospital, New

York City (1934 to 1941 with 1072 cases)[10] and the Free Hospital for Women (1939 to 1943 with 301 cases),[11] compared with the optimum salvage rate suggested by Meigs.[1]

Fig. 4 reveals the survival in the selected group compared with the histologic grading of the carcinoma. It is evident that salvage is about the same in all groups except for a slight reduction in Grade III tumors. Because of the small number of patients in Grade I, however, statistical conclusions cannot be drawn.

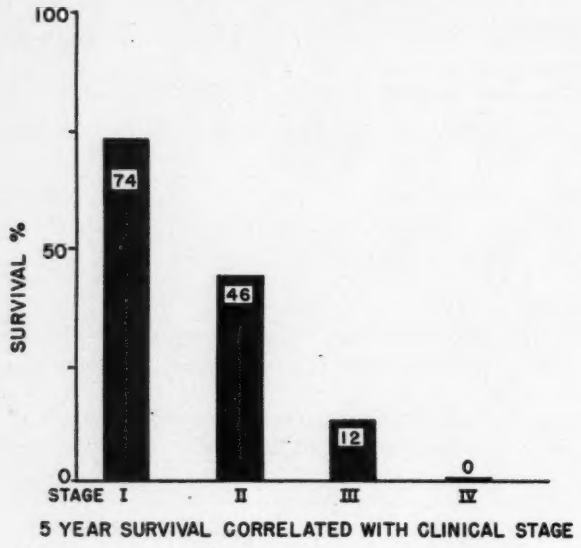

Fig. 2.

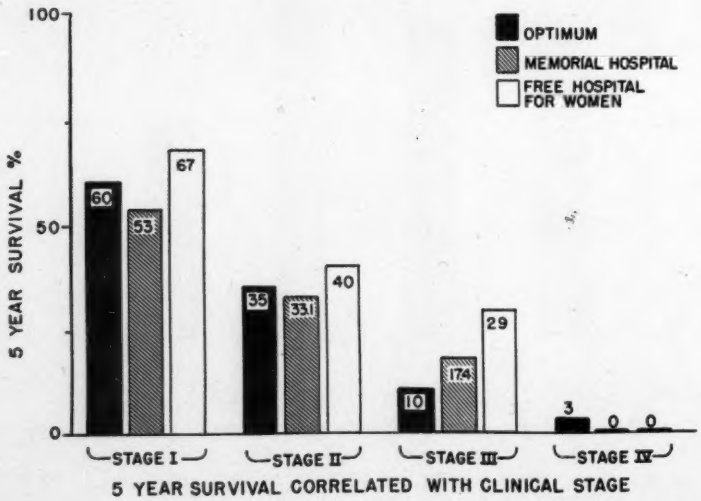

Fig. 3.

5. Radiation Response.—Fig. 5 shows the percentage of cases showing "marked" radiation response in each of the various grades. It can be seen that practically the same degree of response occurred in Grade II and III carcinoma with a somewhat diminished reaction in Grade I and adenocarcinoma.

Fig. 6 compares the survival in patients who evidenced "marked" histologic response and those who showed moderate or minimal reactions.

Fig. 7 shows the per cent of cases in each stage showing marked, moderate, and minimal response. It is evident that there is not a direct correlation between stage and degree of response, that is, radioresistant tumors were not more common in Stages III and IV than they were in Stages I and II, in fact, 88 per cent of the carcinomas in Stage III revealed a marked degree of radiation response.

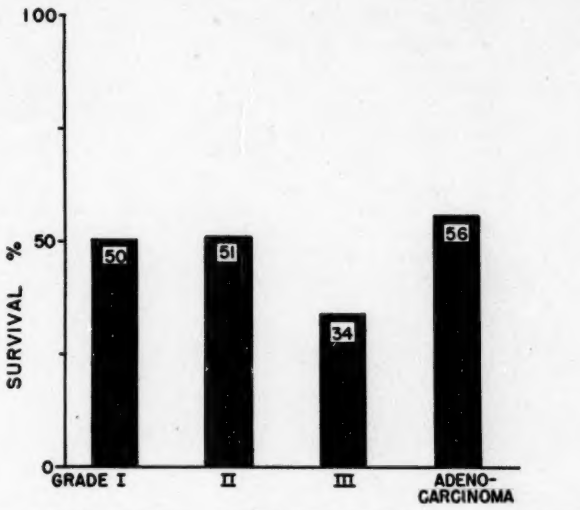

Fig. 4.

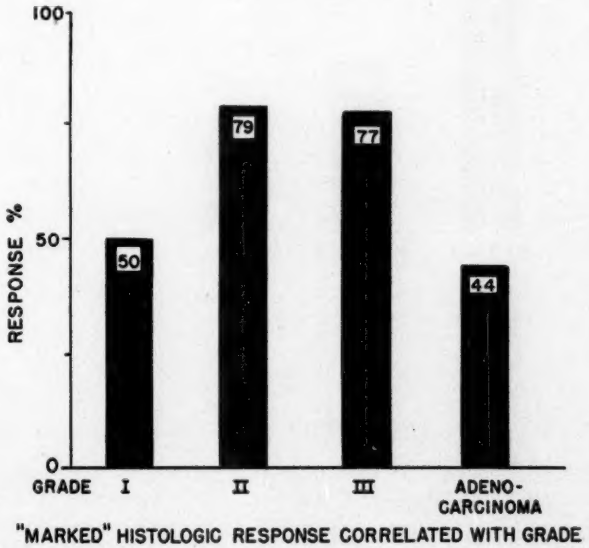

Fig. 5.

Fig. 8 outlines the 5-year survival in those cases showing a "marked" degree of histologic response according to stage. From this graph it can be seen that the survival depended chiefly upon the clinical stage since mortality in Stages III and IV was 100 per cent even with marked response to radiation.

TABLE I. GRADES OF RADIATION RESPONSE IN TUMOR CELLS OF CERVICAL CARCINOMA (AFTER WARREN[6])

	TUMOR CELLS	STROMAL CELLS
Marked response	Mitoses rare or absent Much necrosis Almost all cells abnormal (vacuolated, distorted, swollen) with large hyperchromatic nuclei Only scattered tumor cells	Marked thickening of vessels with hyalinization, necrosis and thrombosis Appreciable increase in fibrosis Marked hyalinization of the collagen
Moderate response	Diminution in mitotic activity Some necrosis Some vacuolization of cytoplasm Readily recognizable tumor	Presence of mild telangiectasis or thrombosis Slight increase in fibrosis Mild hyalinization of collagen
Minimal response	Mitosis undiminished Slight necrosis Slight vacuolization and occasional bizarre form Readily recognizable tumor	Slight telangiectasis No increased fibrosis No hyalinization

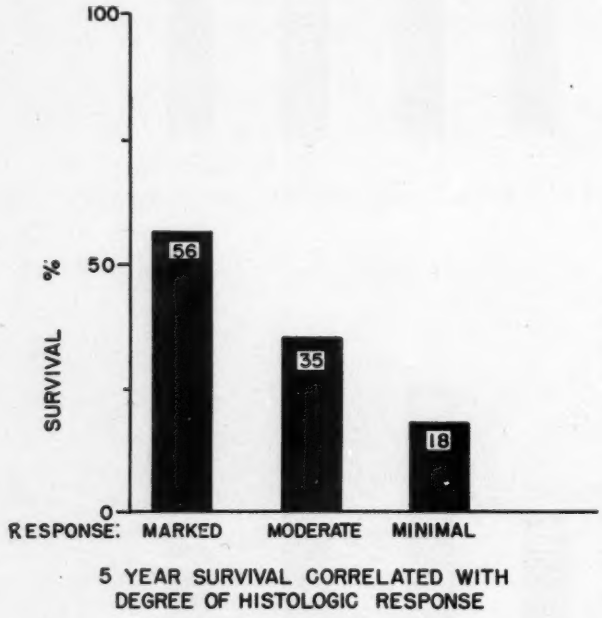

Fig. 6.

Comment

The optimum treatment of carcinoma of the cervix remains a controversial and frequently discussed gynecologic subject. Proponents of the surgical approach have cited the advantages of radical hysterectomy in selected cases but have clearly advised against its general acceptance.[12] Others[13] have described serious sequelae and morbidity associated with radiotherapy. A recent analysis[14] of a statistically significant group of patients has matched and bettered the 5-year survival rates of the leading surgical centers by careful utilization of radium and x-ray together with important general adjunctive measures. Despite the mid-decade tendency toward the adoption of surgery in early cases, irradiation remains, at the moment, the procedure of choice in the majority of patients.

The final decision awaits comparative analyses of larger series with observations over longer periods of time.

It is a well-accepted fact that certain cervical carcinomas possess marked resistance to both radium and x-ray. Theoretically, at least in the earlier clinical stages, radical hysterectomy with lymph node dissection would be of maximal advantage in this group. At the moment, however, no good method exists to predict radiosensitivity or resistance before actual treatment is initiated.

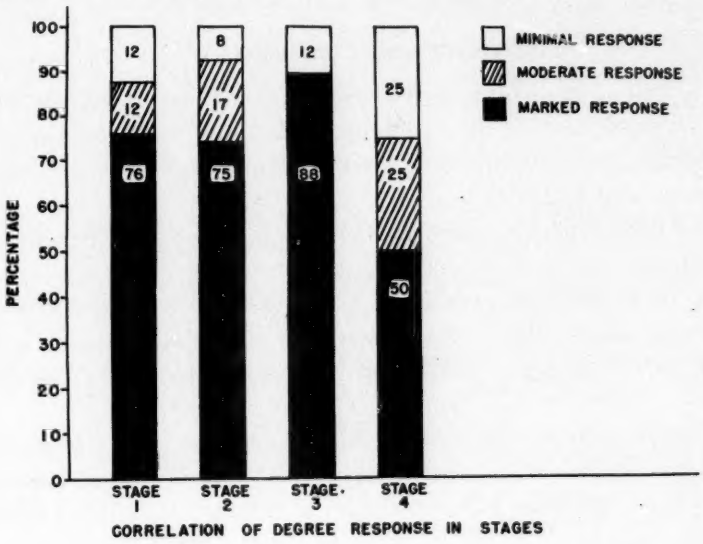

Fig. 7.

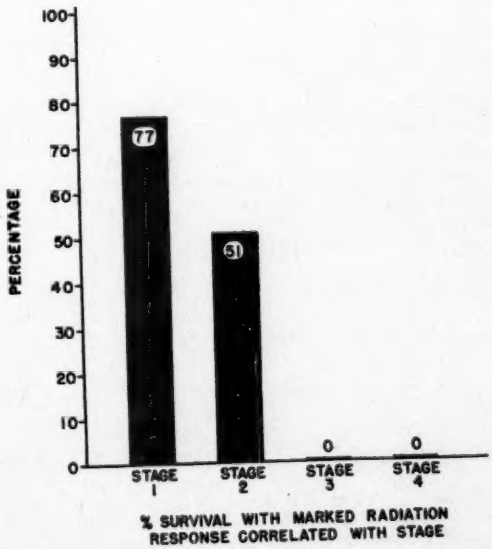

Fig. 8.

Subsequent to irradiation, early and frequent biopsies plus vaginal smears seem to be the only valid criteria available for determination of this degree of tumor response.

We may assume from the foregoing study of postradiation biopsies, that there exists no appreciable difference in the degree of response of Grade II and

Grade III carcinomas (making up the majority of cases) to equivalent irradiation and somewhat less response may be expected in Grade I tumors and adenocarcinoma. In Stage I and II cases, the 5-year survival was increased when a marked degree of radiation response was obtained.

This study suggests that treatment in carcinoma of the cervix does not depend upon the grade of tumor but upon the clinical stage and to lesser extent upon the reaction of the tumor to irradiation. Survival may be improved by utilizing surgery where radioresistance is discovered.

Summary and Conclusions

1. Three hundred fifty-four consecutive cases of carcinoma of the uterine cervix were reviewed and in 100 cases the pre- and postirradiation cervical biopsies were submitted to pathologic study. Tumor response was classified as marked, moderate, and minimal.

2. Grade II carcinoma occurred most often but was not directly correlated with clinical staging.

3. The survival was 50 per cent, and a definite relationship between clinical stage and survival was evident. The survival in each stage compared favorably with figures reported in other institutions and with the over-all series in this hospital.

4. Gradation of tumor does not accurately prognosticate the survival rate.

5. Radiation response of marked degree was somewhat increased in Grade II and Grade III carcinomas, but could not be directly correlated with clinical stage.

6. An increase in survival was evident in patients who demonstrated a marked reaction to irradiation. However, when these cases of marked reaction were analyzed according to stage, the major factor affecting survival was clinical stage rather than degree of response.

7. Surgery is suggested as adjunctive therapy where radiation response is minimal.

The authors wish to thank Dr. George Van S. Smith for his help and suggestions which aided in the preparation of this report.

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AN ANALYSIS OF BREECH DELIVERIES UNDER CONDUCTION ANALGESIA

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SINCE 1943, when Lull and Hingson[1] first popularized the use of conduction analgesia in obstetrics, there have been many controversies over the advisability of using this form of pain relief when the breech of the fetus is the presenting part. We therefore wish to report, in this communication, our experience with conduction analgesia in breech presentation.

During the past five years, from 1945 through 1949, there were delivered at Beth-El Hospital, 438 breeches out of a total of 17,638 deliveries. Not included in this series are babies weighing less than 5 pounds, monsters, and the second of twins when a version was performed. This gives a corrected percentage for breeches of 2.48.

Table I represents an analysis of deliveries for each year.

TABLE I. BREECHES WEIGHING 5 POUNDS OR OVER

YEAR	NO. OF DELIVERIES	NO. OF BREECHES
1945	2918	82
1946	3199	71
1947	4036	95
1948	3683	97
1949	3802	93
Totals, 5 years	17,638	438
		Incidence, 2.48%

Statistics from other clinics throughout the country are given in Table II.

TABLE II. INCIDENCE OF BREECH PRESENTATION (TOMPKINS[2])

AUTHOR	NO. OF DELIVERIES	INCIDENCE OF BREECH PRESENTATION
Moore and Steptoe	51,571	2.8%
Danforth and Galloway	8,531	3.3%
Cannell and Dodek	16,166	3.4%
Morton	8,509	3.5%
Waters	20,000	4.3%
Walsh and Kuder	29,683	4.7%
Patton and Mussey	6,195	4.8%

As may be seen, the incidence of breech presentation at our hospital was low, 2.48. Thus we very nearly approach he percentage of 2.00 as reported by I. F. Cunningham[3] of Dublin in 1945.

In 1934, Gordon and associates[4] reported an over-all survey of breech deliveries in the Borough of Brooklyn. The authors do not feel that the results reported in that paper can fairly be compared with their own results be-

cause of the tremendous strides forward made in obstetrics in the past fifteen years; i.e., wide acceptance of Potter's method of delivering breeches, x-ray pelvimetry, greater use of cesarean section for breeches, and better methods of analgesia. However, Gordon's classification of methods of breech delivery has weathered the years and is still being used at the present time. According to this classification, there are four methods of delivering breeches:

1. Spontaneous and assisted breeches: those deliveries in which the fetus is allowed to deliver spontaneously up to the head. The head may deliver spontaneously or with the aid of Veit-Smellie, Mauriceau, or Wigand-Martin maneuver, or with forceps on the head.

2. Extraction: those deliveries in which the breech is a single or double footling and is delivered by traction on the feet or in which the breech is frank and is delivered as such either manually or by applying forceps to the breech.

3. Decomposition: those deliveries in which the breech is frank and either one or both feet are brought down, usually by the Pinard maneuver.

4. Cesarean section.

Using this classification, we find that the 438 breeches reported in this paper were delivered as follows:

1. Spontaneous and assisted	59
2. Extractions	281
3. Decompositions	72
4. Cesarean sections	26

These may further be subdivided according to the type of analgesia received. (Throughout the paper "conduction analgesia" includes continuous caudal, saddle block, and fractional spinal analgesia, whereas "others" refers to the use of nitrous oxide, ether, local Novocain infiltration alone or in combination.)

		CONDUCTION	OTHERS
1. Spontaneous and assisted	59	10	49
2. Extraction	281	174	107
3. Decomposition	72	59	13
4. Cesarean section	26	25	1
Total		268	170

Therefore it may be seen that 61.18 per cent of patients with breech presentation received some form of conduction anesthesia as compared to the over-all picture at our hospital, where almost 85 per cent of the 17,638 patients delivered in that 5-year period received conduction anesthesia. The reason for this lower incidence of conduction analgesia in breeches is that when caudal analgesia was first instituted, we too were hesitant to use it with our breeches. However, when we saw the excellent results to mother and fetus with caudal (as our paper will bring out), we now use conduction anesthesia with practically the same frequency on breeches as on occiput presentations.

We wish to call attention to the increased frequency of extraction and decomposition under conduction analgesia along with the decreased number of spontaneous deliveries as compared to methods of delivery under other types of analgesia. This we admit is necessary with conduction analgesia and therefore a trained obstetrician is required for delivery. However, we have always maintained that breech deliveries are out of the realm of the general practitioner, regardless of the type of analgesia. Thus conduction analgesia adds no extra burden to this situation.

Material

During 1945-1949, there were delivered at Beth-El Hospital 438 full-term breeches to mothers ranging in age from 17 to 44 years, with an average age of 27.7 years. There were 295 primiparas and 143 multiparas in this group with one maternal death (to be reviewed later). Of these 438 breeches, 268 received some form of conduction analgesia, while the remaining 170 were given some other type of anesthesia.

Results

A. Time of Labor.—In our clinic we found that, contrary to popular belief, conduction anesthesia did not increase the time of labor. Under "time of labor" we did not include the first stage because we felt that this was a very indefinite thing depending upon the emotions of the patient which influenced her acumen in determining when she thought regular ten-minute pains started. For our "time of labor" we computed that rather definite time of the second stage, from the completion of cervical dilatation to the delivery of the baby (Table III).

TABLE III. TIME OF LABOR

TIME OF SECOND STAGE OF LABOR	NO. OF CASES
Conduction Analgesia.—	
Less than 30 minutes	91
30-60 minutes	87
60-90 minutes	40
90-120 minutes	14
120-150 minutes	6
Over 150 minutes	5
Other Types of Analgesia.—	
Less than 30 minutes	96
30-60 minutes	49
60-90 minutes	12
90-120 minutes	3
120-150 minutes	4
Over 150 minutes	4

As may be seen, the time of the second stage of labor is not at all increased under conduction analgesia.

B. Maternal Complications.—These may best be summarized in Table IV.

From Table IV we can readily see that maternal complications were not affected by type of anesthesia; that just as few complications occurred under conduction analgesia as under other types. The one mother who died received continuous caudal anesthesia, but the death was in no way associated with the anesthesia as can be seen from the following synopsis of the case:

C. M., 33 years old, gravida iii, para ii, whose previous pregnancies resulted in normal deliveries of babies weighing 8 pounds, 1 ounce and 8 pounds, 8 ounces, respectively, had her last menstrual period on June 21, 1948, and the expected date for delivery was March 28, 1949. She had a normal prenatal course.

On April 12, 1949, at 4:45 A.M., the patient was admitted to the labor suite with a diagnosis of frank breech position, right sacrum transverse, minus 3 station, 1 and ½ fingers dilated. At 6:45 A.M. the cervix was 4 fingers dilated with the presenting part at plus 1 station. Continuous caudal anesthesia was instituted at this time. At 8:20 A.M. the cervix was fully dilated and the patient was placed on the delivery table. She was delivered by breech decomposition, using the Pinard maneuver to bring down one foot. Piper forceps were

applied to the aftercoming head. The baby weighed 8 pounds, 9 ounces. The third stage of labor lasted five minutes. Inspection of the placenta showed it to be complete. The labor record states that this was "an easy delivery." The patient was transferred to her room.

At 11:10 A.M. the house resident was called to see the patient because of undue bleeding. He found about 800 c.c. of blood and clots in the bed, the patient's pulse was imperceptible, her blood pressure was 50/0, and she complained of weakness. She was neither cold nor clammy. The uterus was found to be soft and relaxed. It was massaged and an ice-bag was placed on the abdomen. An intravenous infusion of 1,000 c.c. of 5 per cent glucose in saline to which 6 minims of Pituitrin had been added, was started. Ergotrate and morphine sulphate were given parenterally. The foot of the bed was elevated. At 12:00 M. transfusions of 500 c.c. of whole blood were started, one in each arm. The pulse rate at this time was 110 per minute; the blood pressure was 60/0. The patient complained of thirst and a few sips of water were given to her. At 12:30 P.M. the transfusion set in one arm broke. By this time the patient had received 400 c.c. of glucose in saline and 400 c.c. of whole blood. An attempt was made to restart the transfusion but this was unsuccessful because of the lack of superficial veins. A cut-down was done but still no suitable veins could be found. The uterus would not remain contracted. As soon as the fundal massaging stopped, it would relax. Oozing continued. At 12:45 P.M. a consultant was called for and he soon responded. However, by this time, the patient was in extremis. Coramine, Adrenaline, and oxygen were administered to no avail. The patient died at 2:00 P.M. A postmortem examination of the uterine cavity showed no rupture of the walls.

This, therefore, was a clear-cut death from postpartum hemorrhage from an atonic uterus and was in no way associated with the type of analgesia or delivery. So the corrected maternal mortality rate in each anesthetic group is zero.

TABLE IV. MATERNAL COMPLICATIONS

CONDUCTION ANESTHESIA		OTHER ANESTHESIA	
Related to Anesthesia.—			
Retained placenta	1	Retained placenta	1
Cervical laceration	2	Cervical laceration	2
Postpartum hemorrhage (one death)	2	Postpartum hemorrhage	1
Cervical dystocia	2	Cervical dystocia	0
Not Related to Anesthesia.—			
Prolapsed cord	1	Prolapsed cord	6
Fibroid uterus	3	Fibroid uterus	1
Pre-eclampsia	5	Pre-eclampsia	4
Postpartum pyelonephritis	1	Eclampsia	2
Postpartum gastroenteritis	1	Partial placenta previa	3
Syphilis	1		
Rheumatic heart disease	1		
Diabetes	1		
Vaginal hematoma	1		

C. Fetal Loss.—Observations of the fetal results with breeches in various clinics throughout the country, as tabulated by Gibson,[5] are shown in Table V.

Our fetal results are shown in Table VI.

From Table VI it may be seen that we had 20 dead infants to contend with, of the 438 breech deliveries. However, when we omit the 10 macerated stillborn infants, the 4 who died of congenital anomalies incompatible with life, and the 1 who died of immaturity, we arrive at a corrected figure of 5

babies whose deaths were directly a result of their breech presentation. Thus our gross fetal mortality is 4.5 per cent and our corrected fetal mortality is 1.1 per cent. This can be further broken down as regards type of analgesia.

TABLE V.

HOSPITAL	AUTHOR	YEAR	FETAL MORTALITY %	
			GROSS	CORRECTED
Johns Hopkins University Hospital, Baltimore	Siegal and McNally	1939	28.1	12.1
Margaret Hague Maternity Hospital, Jersey City, N. J.	Waters	1942	11.2	
Sloane Hospital, New York	Watson	1943	5.2	
Philadelphia Lying-In Hospital	Tompkins	1943	10.4	2.7
Millard Fillmore Hospital, Buffalo	Potter	1944	17.4	9.6
Chicago Lying-In Hospital	Dieckmann	1945	3.8	1.7
	Vogt	1945		4.43
Bellevue Hospital, New York	Heaton and Guyer[6]	1946	30.0	4.5
Finland	Pitkanen[7]	1946	20.8	11.0
Medical College of Virginia Hospital	Ware[8]	1947	5.4	2.7

TABLE VI. FATE OF BABY

A. Related to Anesthesia.—	
1. Conduction anesthesia:	
a. Intrapartum death	1
b. Intracranial hemorrhage	4
c. Neonatal death due to traumatic delivery	1
d. Prolonged resuscitation required	2
e. Erb's palsy	1
f. Ecchymosis and/or cephalhematoma	5
2. Other types of anesthesia:	
a. Intrapartum death	1
b. Intracranial hemorrhage	5
c. Fractures due to traumatic delivery	5
d. Prolonged resuscitation required	3
e. Erb's palsy	2
f. Ecchymosis and/or cephalhematoma	3
B. Not Related to Anesthesia.—	
1. Conduction anesthesia:	
a. Prepartum death (no fetal heartbeart on admission)	5
b. Neonatal death due to congenital anomalies	4
c. Congenital anomalies compatible with life	5
d. Atelectasis	2
2. Other types of anesthesia:	
a. Prepartum death (no fetal heartbeat on admission)	5
b. Neonatal death due to atelectasis	2
c. Neonatal death due to immaturity	1
d. Congenital anomalies compatible with life	6

TABLE VII. FETAL MORTALITY

TYPE OF ANALGESIA	GROSS	CORRECTED
Conduction	4.6%	0.8%
Others	5.3%	1.8%

From Table VIII one notes the decreased incidence of fetal complications when conduction analgesia is used as compared to other types of anesthesia. Table VII shows the rather low figures for corrected fetal mortality in breech deliveries which the Beth-El Hospital has attained.

TABLE VIII. FETAL INJURIES

	CONDUCTION (%)	OTHERS (%)
Intracranial hemorrhage	1.6	2.9
Fractures	2.0	2.9
Prolonged resuscitation required	0.8	1.8
Erb's palsy	0.4	1.1
Ecchymosis and/or cephalhematoma	2.0	1.8

D. Cesarean Section.—Of the 438 breech deliveries, 26 were terminated by cesarean section. Fractional spinal anesthesia was used in 25 of these and nitrous oxide in one. The indications for these sections are as follows:

Fetopelvic disproportion	18
Cervical dystocia	2
Uterine inertia	2
Placenta previa	2
Previous section	1
Cardiac condition	1
	26

Our incidence of cesarean section in breech presentations is 5.9 per cent as compared to the over-all percentage of 3.5 per cent sections for all types of presentations at the Beth-El Hospital. Our incidence of cesarean section for breeches, therefore, is higher than our over-all incidence for sections, but this is in agreement with other clinics which report incidences as high as 13.7 per cent (Mayer[9]) and 27.9 per cent (Dennen[10]) cesarean sections for breeches.

Comment

Since 1943, when continuous caudal analgesia and saddle block in obstetrics were first instituted at our hospital, the obstetricians there have used conduction analgesia with increasing frequency for their cases of breech presentation; this, despite the protestations of many obstetricians and conduction analgesia enthusiasts who stated that breech presentation was a contraindication to the use of caudal anesthesia. The increasing use of conduction analgesia for breeches was not done by us in a haphazard fashion. We used it cautiously at first; but when case upon case and statistics upon statistics were added up, we saw that results were excellent—that breech presentation per se offered no contraindication to the use of conduction analgesia. We had read that conduction analgesia does away with the mother's expulsive efforts and so she does not voluntarily expel the baby. Therefore a caudal should greatly increase the time of labor. That caudal eliminates the mother's expulsive force is true but that time of labor increases does not follow. With or without caudal, cervical dilatation occurs and when this is complete, the delivery may be accomplished by extraction or application of low forceps or decomposition even in the absence of the mother's "pushing power." Our statistics have shown that when the mothers are able to bear down, 93 per cent of them will have second stages of less than 90 minutes as compared to mothers who are given caudal and cannot bear down where 90 per cent have second stages of less than 90 minutes. The figures, therefore, are practically equal, and the authors are certain that all will agree that those mothers having caudal are a great deal more comfortable during the second stage of labor.

In our series, there was no significant difference in the complications affecting the mothers in either the conduction-analgesia group or in the other group. Postpartum hemorrhage, retained placenta, etc., occurred with equal frequency under both types of analgesia. But of course, the mothers with

conduction analgesia were more comfortable, more secure, more cooperative, less frightened, and less exhausted than the mothers who received no conduction analgesia.

Although the categories of "time of labor" and "maternal complications" show no significant differences as far as type of analgesia employed is concerned, the statistics for "fetal results" are greatly in favor of caudal. The incidence of intracranial hemorrhage, traumatic fractures, Erb's palsy, and prolonged resuscitation (all common occurrences with breeches) are all markedly reduced by conduction analgesia. And when we compare our corrected fetal mortality for breeches (0.8 per cent, Table VII) with those reported by other clinics (Table V), it is seen that we have one of the lowest figures reported. Credit for this must be given to our use of conduction analgesia. Labors with breech presentations are, for the most part, long affairs—usually several hours longer than labors with occiput presentations. During this time, the mothers must be given one or two or more periods of relief from pain by any one of a number of pharmacological methods, or else she will soon exhaust herself. Barbiturates, morphine, Demerol, chloral hydrate, etc., all ultimately cross the placental barrier and cause some degree of narcosis in the fetus. When these are used over a prolonged period of time and are topped off with a general anesthetic such as nitrous oxide, ether, chloroform, or cyclopropane at delivery time, such a combination of events will lead to an increase in fetal mortality. The advantage of continuous caudal analgesia is that it may be given over a long period of time (we have had caudals lasting 2, 3, 4, 6, and even 10 hours) with complete pain relief to the mother and with no effect at all upon the fetus. In addition, in the great majority of cases, the caudal is enough to eradicate the pains of delivery too, with no additional general anesthetic necessary. We agree with Hingson and associates[11] that with caudal there is an "earlier spontaneous onset of respirations" by the baby and a "diminished need for special agents to induce respirations." "Caudal babies are more alert and wide awake."

Summary

We have attempted to show, in this paper, that there are definite advantages to the use of conduction analgesia for breech presentations. Our statistics show no increase in time of labor nor in maternal complications when conduction analgesia is used. On the other hand, our statistics also show a decreased fetal mortality under conduction analgesia with a decrease in the number of complications to the infant. These, in addition to the greatly increased comfort to the mother, are definite points in favor of this method of pain relief.

The authors by no means wish to make the point that conduction analgesia is the answer to all breech labors. It is not. Administration of a caudal is comparatively a difficult thing. To administer a caudal takes a highly trained technician, and to give a large number of caudals in a busy obstetrical hospital takes a smooth-running system. Given a hospital geared to this set-up, the authors are in full agreement with Hingson and Lull,[1] with Nicodemus,[12] and with Lloyd[13] that conduction analgesia is the ideal form of analgesia for breech deliveries.

We wish to thank the Obstetrical Staff of the Beth-El Hospital for making the records of their private cases available to the authors.

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USE OF CESAREAN HYSTERECTOMY*

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PRIOR to the period of this report, cesarean hysterectomy had been performed by the writer, as by every obstetrical surgeon, in cases were pregnancy had developed with the co-existence of massive fibroids in the uterus; also, where abruption of the placenta had caused extensive infiltration of blood through the uterine wall into the parametrial tissues. In these cases removal of the uterus was a matter of necessity. In the past seven years the practice of hysterectomy following cesarean has been more often a procedure of election. Discussion of the broadening indications for employment of this operation is the main purpose of this presentation. Satisfactory postoperative course and follow-up are noted as important considerations in assessing whether this trend is good or otherwise.

Statistics are compiled from the obstetrical departments of two general hospitals of similar size and organization. Twenty-seven of the 41 cases here reported were my private patients followed throughout the antepartum course. Three were patients of other doctors, referred after complications of labor were recognized. Nine were on ward service, also eventually seen and operated on by me. The remaining two patients with fibromyomas of the uterus were operated on without consultation by the chief of the general surgical service.

All of these patients, it is believed, deserved cesarean delivery. The presumptive advantage of removal of the uterus or the desirability of some sterilization procedure did not dictate the abdominal section.

Three cases of rupture of the uterus before or during labor are not included in this report because the procedure of hysterectomy was mandatory and cannot be strictly titled cesarean hysterectomy.

TABLE I. MONMOUTH MEMORIAL AND FITKIN MEMORIAL HOSPITALS, MONMOUTH COUNTY, NEW JERSEY

	TOTAL NO. PATIENTS DELIVERED	ALL CESAREANS	INCIDENCE PER CENT	MORTALITY	CESAREAN HYSTERECTOMY	INCIDENCE PER CENT OF ALL "SECTIONS"	MORTALITY
1943	2,203	38		1	4		0
1944	2,187	59		0	5		0
1945	2,140	51		1	6		0
1946	2,815	66		0	4		0
1947	3,362	99		0	7		0
1948	3,065	102		0	8		0
1949	3,059	94		0	7		0
	18,831	509	2.7	2, or 0.4%	41	8	0

*Presented at a meeting of the New York Obstetrical Society, Nov. 14, 1950.

As noted in Table I, the number of cesarean hysterectomies was 8 per cent of the total of cesareans in the seven years of this study. As with every obstetrical technique, usage varies widely in different clinics. I think that this is explained by factors of training, experience, attitude, or philosophy and possibly by religious principle because of the interference with childbearing function rather than by the worth of the procedure. For example, in the seven-year period covered by this study our friends at the Margaret Hague Hospital performed hysterectomy after cesarean section only 23 times. The total number of cesareans was 2,047 so that the incidence was only 1.1 per cent. In the conservative Boston tradition, statistics from the Boston Lying-in Hospital for the ten years prior to 1945 reported by F. C. Irving[2] showed 46 hysterectomies constituting 1.8 per cent of all cesareans, not including cases of rupture of the uterus. In 1945 also, Karl Wilson[1] of the University of Rochester reported 31 Porro operations in a total series of 331 cesareans, an incidence of 8.7 per cent. A series of 54 cases reported by Reis and DeCosta[3] from the Michael Reese Hospital represented 4.5 per cent of the total number of cesareans for a twelve-year period prior to 1945. This paper by Reis and DeCosta, published in 1947, reviews admirably the history of the Porro operation and describes the modified technique now generally followed to accomplish supracervical ablation of the uterus after cesarean delivery. Dieckmann, Bjork, and Aragon[4] have described the largest number of cesarean hysterectomies which has come to my attention, i.e., 153 cases over a fifteen-year period at the Chicago Lying-in Hospital (1931-1947). During these years there were 46,949 deliveries and 2,444 cesarean sections (5.2 per cent). The cesarean hysterectomies represent 6.3 per cent of the total number of cesareans. For the last 5½ of the 15½ years the incidence was 7.8 per cent. There was one fatality in this series.

Total hysterectomy was performed in only one of our 41 cases. The rest were supracervical hysterectomies. In the earlier years of the series the preservation of some endometrium was planned. More recently, the line of amputation has been well below the internal os. It can be argued that danger of malignant change in the cervical stump makes anything but total hysterectomy an indefensible procedure. But in the fairly large number of patients subjected to emergency operation, any steps which would prolong anesthesia and increase surgical shock would be unwise. Also, the patients long in labor with retracted, dilated cervices present special difficulties in accomplishing total hysterectomy. It is my prediction that the ratio of complete hysterectomies will increase, but insistence upon extirpation of the cervix in every case will invite disaster and place the operation in disrepute. We do not expect to lose touch with these patients. Regular inspection of the cervix is recognized as essential along with treatment of infection or other pathologic conditions, if present. Cervicectomy was performed on one patient of this series along with repair of cystourethrocele, a year or more after the cesarean hysterectomy. This service can be offered to others if necessary.

TABLE II. INDICATION FOR HYSTERECTOMY FOLLOWING CESAREAN SECTION

1. Fibroids	10
2. Antepartum hemorrhage	5
3. Toxemia (chronic nephritis)	3
4. Dystocia in multipara, infection presumed	7
5. Uncontrollable bleeding at cesarean	1
6. Multiple or unsatisfactory cesarean scars	7
7. Physical and psychic trauma in previous delivery, prolapsus, menorrhagia, etc.	8
	41

Table II shows the indications known before interference or conditions found at the time of operation which made hysterectomy seem advantageous for the patient's immediate safety or future well-being. As would be expected, determining factors were often multiple and that noted was only one of several in many cases. The first five groups may be termed the usual or generally recognized indications. In the sixth and seventh groups are the cases where reason for removal of the uterus has been less well established or accepted by the profession. The decision was made only after close and conscientious study of each patient. As previously stated, opportunity to effect protection against another pregnancy was not a primary objective of abdominal section nor was hysterectomy performed as advocated by Lazard[5] of Los Angeles and others as the routine method of sterilization.

All of the women in this series were over 30 years of age. Twenty-nine of the 41 were more than 35, and six had passed the fortieth birthday. Except four primigravidas with massive myomas, all had one or more living children before this delivery.

1. Fibroids.—These 10 patients do not constitute a large percentage of all with palpable fibroids in the pregnant uterus. It should not be thought, therefore, that this method of management is the usual one. The four women who were having their first babies were given a trial labor. Membranes were ruptured in three of the four cases. Two of these patients had been unable previously to conceive although married for many years. One was 32, two were 34, and one 38 years of age. With unsatisfactory progress in labor, and the fate of the baby so very important, abdominal section seemed the conservative procedure. The other six in this group had one to three children each. One had had two previous cesareans. Another was pregnant at age 38 after having three deliveries in her early twenties. In this case, the birth canal was now obstructed by a tumor. In another case the interference was an emergency measure dictated by severe pain and hemorrhage. Although the uterine mass weighed 14 pounds and the placenta was partially separated, the premature infant was salvaged. The three remaining patients in this group were over 35 years of age. Each had long been aware of the presence of fibroids and was most anxious to be relieved of the tumors as well as desirous of protection against future pregnancy.

2. Antepartum Hemorrhage.—Five patients operated on to control severe antepartum bleeding were subjected to hysterectomy. The youngest of this group was 32. She had four living children. The others were multiparas, 36, 37, 42, and 44 years of age. Two had central placenta previa, the other cases were major abruptio placentae. Three of these women were admitted in very poor condition with almost complete exsanguination. Operation was undertaken only after blood replacement and other treatment for shock. Need for haste was fully appreciated but removal of the uterus seemed the only way to guard against additional blood loss that might weight the balance against recovery. Reports of other observers justify this procedure in these cases of desperate emergency. Operative shock appears not to be greater and the uphill postoperative climb seems more certain and steady. There is comfort in knowing that the blood which must be infused is not going to be lost from the relaxed uterus. One of the two fatalities which mar our cesarean statistics was the death of a primigravida with central placenta previa and violent hemorrhage. Abdominal section was promptly done and several transfusions given but shock persisted until death, twenty hours after the operation. I believe that bleeding was never completely controlled.

3. Toxemia (Chronic Nephritis).—There are three instances here of necessary interference before term because of severe toxemia. In two cases, long-

standing kidney damage was known. One of these women had a cesarean to terminate her first pregnancy under similar circumstances. Although chronic nephritis is listed as an indication for hysterectomy by other writers, I removed these uteri to make sterilization permanent and absolute.

The third patient was a 230-pound Negro woman, aged 30 years, the mother of eight children. She was eclamptic when admitted to the hospital and remained comatose for many days. After some improvement in her condition, attempts to induce labor were made without success. Hysterectomy had the double objective of eliminating potential intrauterine infection and preventing further pregnancy.

4. Dystocia in Multiparas, Infection Presumed.—Dystocia for various reasons was the common factor in this group. Intrauterine infection was at least a strong probability. Had these women been young and without a family, extraperitoneal cesarean section might have been done. My experience with this operation dates back many years to early teaching by the late Dr. Jellinghaus, and results have been entirely satisfactory. But I am impressed by the contention of Dr. Dieckmann and others that removal of the uterus is the surest way to protect the frankly infected patient. Likelihood of excessive postpartum bleeding was great in most of these cases due to overdistention and fatigue of the uterine musculature. So here again the management of these problems was the result of mixed motivation.

Study of these seven cases illustrates what every obstetrician of experience knows well, namely, that a record of successful deliveries is no guarantee of uncomplicated labor. Rather do the difficulties and dangers of parturition increase with multiparity. The "grand multipara" is frequently obese and hypertensive. Relaxation of the abdominal wall invites malpresentation of the fetus. Scarring of the cervix may be a barrier to dilatation or the cervix may tear extensively and cause profuse bleeding. An oversize baby is not uncommon. Two of the women in this group, one a para vii and the other para viii, were badly neglected on ward service. Both labored for days with ruptured membranes without making satisfactory progress. In each case life of the baby was lost during labor. One infant weighed 5,500 grams, the other 5,220 grams. The failure of the uterus to rupture in these cases was most fortunate. The other five women also made poor progress in labor, one with a baby weighing 5,000 grams, two with babies over 4,000 grams. One, aged 44 years, had not been pregnant for 18 years and had real cervical dystocia. Another, aged 37, came to my care after many hours of labor with the child transversely in the uterus and membranes ruptured.

5. Uncontrollable Bleeding at Cesarean.—Other than premature separation of the placenta, which has been separately considered, a number of complicating conditions may cause excessive bleeding during or after cesarean section. In 1941, for example, N. B. Sackett read before this Society a most interesting case report of uterine atony and hemorrhage following cesarean delivery. Hysterectomy was necessary and pathological study showed extensive adenomyosis of the uterus. It may be wise to explore the uterine cavity in all cases of cesarean section. Fragmented or abnormal placental tissue, a submucous fibromyoma, or a rent in the uterine wall may be found. But my case problem was not one of these. The patient, aged 32, had a primary elective classical cesarean for cephalopelvic disproportion in another hospital. She was short and obese with a contracted pelvis of android type. Repeat section was planned. When labor began sharply two weeks prior to term, the operating room was hastily set up. Spinal anesthesia was objectionable to this highly excited patient and Pentothal Sodium was employed. Choice of anesthesia was unfortunate. The abdominal wall was poorly relaxed and extremely fatty. The fetal head had descended through the pelvic inlet. In hurrying to bring

the head up through the low segment incision, a lateral tear resulted and there was sharp bleeding from the uterine artery or a main branch thereof. Hysterectomy was thought to provide safer hemostasis than repair, especially since the patient and her husband had signed a request for sterilization.

6. Multiple or Unsatisfactory Cesarean Scars.—Before discussion of this group of "repeat cesareans," it may be of interest to state that we do not subject all patients with previous hysterectomy to reoperation. The record of many years shows almost one-third of all such cases in our hospitals delivered through the birth canal without accident. The nature of the scar in the uterine wall cannot be anticipated with accuracy even though data concerning the technique previously employed, postoperative morbidity, etc., are available. Because of the uncertainty of the conditions which may be found, it is my practice to have permission for sterilization signed by the patient and her husband before operation, even though I hope not to employ any procedure to this end, regardless of the number of cesareans.

In six of the cases in this group, very thin scars were indicative of poor healing of previous incisions and the conditions present seemed to constitute pathology. The seventh patient had three cesareans prior to this final pregnancy, and the tubes had been ligated after the third.

7. Physical and Psychic Trauma in Previous Delivery, Prolapsus, Menorrhagia, Sterilization Desirable.—There are eight cases in this group, all of them my private patients, known and treated for various pelvic complaints before the final pregnancy. Six were over 35 years old. Because the indication for operation may be questionable, I wish that there were time to report the circumstances in detail. To be brief, I can point out several common factors. Each of these women had experienced at least one severely traumatic labor. All had extensive injuries to the tissues of the birth tract and relaxation of the fascial supports of the uterus that caused annoyance or disability. Three of the group had already submitted to extensive cervical and vaginal repair. Menorrhagia and dysmenorrhea were distressing to several of these patients, indicating intrinsic pathology of the uterus or marked varicosity of the pelvic veins. Every one had a serious dread of another difficult obstetrical experience. At least three patients invited this final pregnancy with definite understanding that a cesarean would be performed. At the time of operation special attention was given to utilizing the sacrouterine ligaments in support of the cervical stump although plication of the sacrouterine folds was a routine procedure in all cases. In one case the cervix was extirpated with the uterus. Secondary reconstructive vaginal surgery was accomplished in three cases on the eighth day after cesarean hysterectomy.

TABLE III. CESAREAN HYSTERECTOMY

Anesthesia	
Spinal	30
General	9
Pentothal Sodium	2
Postoperative morbidity	5 (12%)
Discharge	Average 10th day
Secondary reconstructive surgery	4
Incidental surgery	5

I have been able to observe closely the progress of these patients. It is fair to say that without exception their mental and physical outlook has improved greatly. It is a satisfaction that this rehabilitation has been accomplished with a minimum of time lost from family responsibilities and with minimal hospital and medical expense. Few of these patients could have readily arranged elective pelvic surgery.

Methods of anesthesia employed are noted for possible interest. We are well satisfied with "spinal" in elective cases. Time consumed in performance of the operations here reported varied from 40 to 60 minutes. The postoperative course was remarkably smooth in the great majority of cases. Moderate elevation of temperature was noted in five cases. Three patients had gastric dilatation and ileus necessitating Wangensteen drainage. One of these also became profoundly anemic and received three transfusions of one pint each. It was presumed that there was imperfect hemostasis in this case. One or more transfusions were given to nine other patients, five being those with antepartum hemorrhage.

When the time of operation could be chosen, the usual preoperative measures were taken including withholding of food for eighteen hours before the hour set. In all cases, blood studies were made and blood held in readiness for transfusion. Postoperative management has been routine also. Activity of the patient in bed has always been encouraged and in recent years ambulation after 48 hours has been permitted. Antibiotics are ordered in special cases only. There has been no instance of suspected thrombophlebitis.

Day of discharge from the hospital varied from the eighth to the fifteenth day except in the four cases where secondary cervical and vaginal repair was performed. The incidental surgery consisted in the removal of a rather sizable ovarian tumor, previously undiagnosed, in three cases, unilateral salpingoophorectomy in one case where a disturbing hematoma developed in the broad ligament after suturing, and appendectomy in one case.

Follow-Up.—Thirty-one of these patients have been regularly seen and recently examined. Ten of this number report regular "menstruation" evidenced by slight spotting for a day or two. There has been no expressed regret that the removal of the uterus was necessary. No regular or serious pelvic discomfort has been brought as a problem. Certainly the group of women who formerly dreaded each "period" are now happily comfortable.

With respect to marital relations, there has been a decided and uniform improvement. The increased appreciation of the sexual intimacies may be due in some measure to the freedom from fear of pregnancy, but it is dependent also, I am sure, upon lessened fatigue and greater sense of well-being.

Office examination of these women shows the cervical stump well suspended and free from evident pathology. In the one case of total hysterectomy, findings after one year are satisfactory.

Two additional patients responded to written inquiry with statements that they are "all right."

Conclusion

The personal experience of seven years in performance of hysterectomy following cesarean section has been reviewed. This relatively easy and safe operation controls intrauterine infection, eliminates danger of postpartum bleeding (from the placental site), removes intrinsic pathology of the uterus, and accomplishes positive prevention of further pregnancy. I submit that great advantage can be expected also from its employment in cases of marked relaxation of the uterine fascial supports and severe pelvic varicosities. For families in the low income group, often with several children, restoration of the mother's health at minimal cost and with the least possible loss of time coincident with safe delivery of a baby is no small accomplishment. Hastening of menopause symptomatology has not been observed. The danger of leaving the cervical stump is not unappreciated. It is believed, however, that pan-

hysterectomy under conditions present late in pregnancy is too hazardous for routine use. Watchfulness of the cervix and removal at a later date if necessary should safeguard the patient.

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Discussion

DR. EDWARD G. WATERS, Jersey City, N. J.—I think it is clear from the tables and from Dr. MacKenzie's comments that the majority of these hysterectomies had a motive of sterilization. I would also believe that most of these patients were multiparas in whose cases the factor of more pregnancies did not enter too greatly. Cesarean hysterectomy for fibroids at Margaret Hague Hospital is largely confined to cases of obstructing tumors, patients in the last part of the childbearing years who are multiparas and who distinctly wish the childbearing potential terminated, having had a sufficient number. I am sure Dr. MacKenzie does not wish us to believe that all sectioned patients with fibroids should have a hysterectomy, inasmuch as conception and parturition occurred in spite of the pathology, and such uteri may successfully harbor two or three more pregnancies. That point is worth emphasizing and I am sure Dr. MacKenzie would be in agreement.

If anyone is interested and does not already know, I suggest a review of the figures at the Margaret Hague Maternity Hospital on extraperitoneal section with retention of uterus, with Dr. Dieckmann's figures on extirpation of the uterus. Our patients can get pregnant again but the victims of the Porro never will, and we have just as high a percentage of salvage. Regarding hysterectomy for placental abruption and hemorrhage, as for as our institution is concerned, I will say that in a ten-year period comprising just under 74,000 deliveries and 2,628 cesarean sections, an incidence of about 3.4 per cent, with 23 hysterectomies, or 0.3 per cent, we had one cesarean hysterectomy for bleeding. That was a case of placenta previa with a complicating accreta with persistent postcesarean hemorrhage. That patient died and that is the only death from hemorrhage we had in eight years from placenta previa and abruption of the placenta. I would very much question any change in our policy which in any way might increase the number of cesarean hysterectomies for bleeding due to placenta previa or abruption since in this volume of work there was required but one such operation in an eight-year span.

One other point that I would like to have cleared is how a supravaginal hysterectomy will help any prolapse or relapse relaxation. That I cannot understand from an anatomic or operative standpoint.

DR. ANTHONY D'ESOPO.—Last year before this Society I reported our experiences with the cesarean section operation at Sloane Hospital, at which time 53 cesarean hysterectomies were noted in the total group of 1,000 cases, making an incidence of 5.3 per cent, which closely approximates the incidence reported by Dr. MacKenzie.

In the majority of our cases the uterus was removed because of fibromyomas, which is undoubtedly the principal reason for this procedure in any modern series of cases. It was also of interest to note that some twenty of the hysterectomies were done primarily to achieve sterilization. However, a majority of these fitted into the special group brought out by Dr. MacKenzie. They presented some dysmenorrhea or metrorrhagia. It was felt that the uterus could be conservatively sacrificed in these cases. I feel that we will do this operation more often instead of sterilization by tubal ligation when such symptoms are

present. It seems very logical to broaden our indications in this way because the cesarean hysterectomy is equally as safe as the low flap operation.

Another group of cases that should be more seriously considered for this procedure are those in which hemorrhage is the presenting indication for the cesarean section and, more particularly, the cases of placenta previa. Hysterectomy for accidental hemorrhage has been overemphasized but little has been said about its importance in placenta previa. Placenta previa is a disease of the multipara. She has frequently had her family and when we operate it is often far better to do a cesarean hysterectomy than a tubal ligation. We have had the unfortunate experience of being forced to reopen the abdomen to remove a uterus after a cesarean section for placenta previa had been completed. During the hour after the patient was put back to bed, she developed a massive vaginal hemorrhage which resulted in profound shock and her life was saved only by the most vigorous antishock therapy and hysterectomy.

DR. MACKENZIE (Closing).—I have opportunity now to correct an apparent misunderstanding. Hysterectomy has been found necessary in only a small proportion of our cases of central placenta previa and major abruptio placentae. Like Dr. Waters I have never been intimidated by the appearance of the Couvelaire uterus. Each of the six patients reported in the "hemorrhage" group were in such desperate condition that removal of the uterus was considered a measure to save life by positively arresting blood loss. Dr. Heaton shrewdly questioned the procedure followed in the cases of cesarean section for toxemia and chronic nephritis. In one of the three patients other indications than the need for prevention of pregnancy amply justified the hysterectomy. In the other two I admit that partial or complete salpingectomy might have been the better course.

The experience of Dr. Davis in removal of the cervix with the uterus after cesarean section is valuable. I shall not attempt to answer Dr. Waters' intimation that removal of the uterus and support of the cervical stump combined with vaginal wall repair fail to correct retrodisplacement and partial prolapse of the uterus. The follow-up in the eight cases reported seems convincing to me.

It is most gratifying that none of the speakers have insinuated that I take any satisfaction in terminating the childbearing function. I am an enthusiast for large families. In most instances reported here sterilization was the inevitable corollary of surgery to preserve life and health.

A NEW BIOCHEMICAL TEST FOR PREGNANCY*

A Study of 2,560 Tests on 1,640 Patients

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THE importance of the early diagnosis of pregnancy is not open to question, but the means of accomplishing this end are slow, unwieldy, undependable, or costly in time, money, and materials. Evidence substantiating this fact is that there are today approximately forty tests for pregnancy, including chemical, biochemical, and biological methods. Scientifically and medicolegally, the importance is obvious.

Efforts at diagnosis of pregnancy have progressed from the recognition of the first missed period, the presumptive signs and symptoms, through the finding of the Hegar sign, the Abderhalden reaction, and various physiological changes, to our modern biological and chemical methods of making diagnosis earlier and more accurate.

Today a procedure for the diagnosis of pregnancy is of little value unless it offers an accuracy approaching that of perfection. With this goal in mind, the author has worked over a five-year period to develop a biochemical pregnancy test of high dependability, simple to perform, and requiring a minimum of time, equipment, and expense. The result achieved is a biochemical test of pregnancy, which is the subject of this paper, requiring only two special test tubes and four reagents. The technique is so simple that the physician, nurse, or technician can perform the test in thirty minutes or less. The diagnostic reaction is a distinctly brown color which can be read with the naked eye, without mechanical aid, such as ampules, polarimeter, spectroscope, regular colorimeter, or photoelectric colorimeter.

The convenience of the test is obvious, inasmuch as animals are totally unnecessary for the test and their cost, caging, refrigeration, or other care is entirely eliminated. No autopsy, biopsy, or other technical examination is required.

The chemical test, furthermore, must be as dependable in its negative as in its positive findings. This presented a problem in working out the chemical factors since the essential reagent gives positive results for several of the sex hormones. After early studies produced an accuracy approaching 100 per cent in known pregnancies, there still remained a 50 per cent positive error in nonpregnant individuals. Further study employing various hormonal extractives brought to light the fact that in the nonpregnant individual, two endocrine factors gave a positive response. This necessitated the development of an extractive method by which the interfering agent could be removed. With this

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accomplished, both positive and negative responses were obtained and a simple, easy procedure of approximately 100 per cent accuracy for both pregnant and nonpregnant subjects resulted.

The product of pregnancy, which is identified by this test, is free estrone. While estrone is found in the normal nonpregnant individual, it is, however, not present in a sufficient quantity to cause a positive response, since the essential reagent used is calibrated to such strength that it does not produce a positive reaction with the lesser amount of free estrone present in the nonpregnant individual. There are two pathological conditions, however, which produce a positive reaction, namely, hydatidiform mole and chorionepithelioma. As with the biological tests, the response in these conditions is quite significant and they are positive with very high dilutions of urine. The simplicity of the test is also of advantage in diagnosing complete recovery from these conditions as indicated by negative reactions.

Method

The diagnostic agent used in identifying free estrone is 2, 4-dinitrophenylhydrazine in solution in ethanol. Estrone also may be identified by the use of meta-nitrobenzene in ethanol, this latter giving a reddish-violet color instead of brown. The metanitrobenzene reaction, however, was found in this study to be far less reliable because of its response to various medications, especially acetophenetidin. Such false reactions are not experienced with 2, 4-dinitrophenylhydrazine, which is the standard activating agent in this test. Both methods will be described and both are alike, except in the final steps of procedure.

Most of the chemical tests of pregnancy previously employed have been based upon the identification of histidine. While histidine is increased in pregnancy, it, nevertheless, lacks the specificity found in the free estrone increase. The Kober phenolsulfonic color reaction,[1] based on the quantitative determination of estriol, required 24 hours. The Kapeller-Adler reaction[2] is based on the presence of histidine. Dodds,[3] reporting on the Visscher-Bowman test for pregnancy, found 90 per cent accuracy in the pregnant, and but 88.8 per cent in the nonpregnant individual. Soule and Yanow[4] reported an accuracy of 96.5 per cent for the Guterman reaction, while Reinhart and Barnes[5] found it negative in 16.4 per cent of pregnant women in their series, and positive in 42 per cent of those not pregnant. Of all their positive results, 27.7 per cent were false and of all the negative results, 27.5 per cent were false. These latter investigators attributed the high error to the variation in progesterone metabolism in both pregnant and nonpregnant women. Such errors are eliminated in this biochemical test by the extraction of progesterone.

The Ricketts, Carson, Saeks[6] test for the early diagnosis of pregnancy, according to the authors, is based upon a substantial excretion of histidine in normal pregnancy. The authors report a total accuracy of 94.2 per cent, or an error of 5.8 per cent. The total series included 431 tests, 406 of which were correct. Of 268 pregnant individuals tested, 255 tests were correct, or 95.1 per cent, with an error of 4.9 per cent. Of 162 nonpregnant individuals tested, 151 tests were correct, or 92.6 per cent, with an error of 7.4 per cent. In this series, only 26 pregnant women were tested in the first month, with an error of 7.5 per cent, while in 31 nonpregnant women, the error was 3.3 per cent. Sixty-nine tests in the second month showed an error of 1.3 per cent in pregnant individuals, while in 10 nonpregnant controls the error was 30 per cent. Other cases reported showed corresponding variability of error.

In their summary of the reasons for error, the authors attributed false results to six causes, as follows:

1. Lack of control of protein intake prior to test.
2. Tests on too dilute specimens.
3. Disappearance of histidine in eclampsia.
4. Endocrine disorders of thyroid, pituitary, and adrenal glands lessening the specificity of the test.
5. Amino acid excretion in impaired hepatic function.
6. Nutritional deficiencies, causing weak positive or false negative results.

These reasons appear rather extensive in number, and cast doubt upon the dependable accuracy of their pregnancy test.

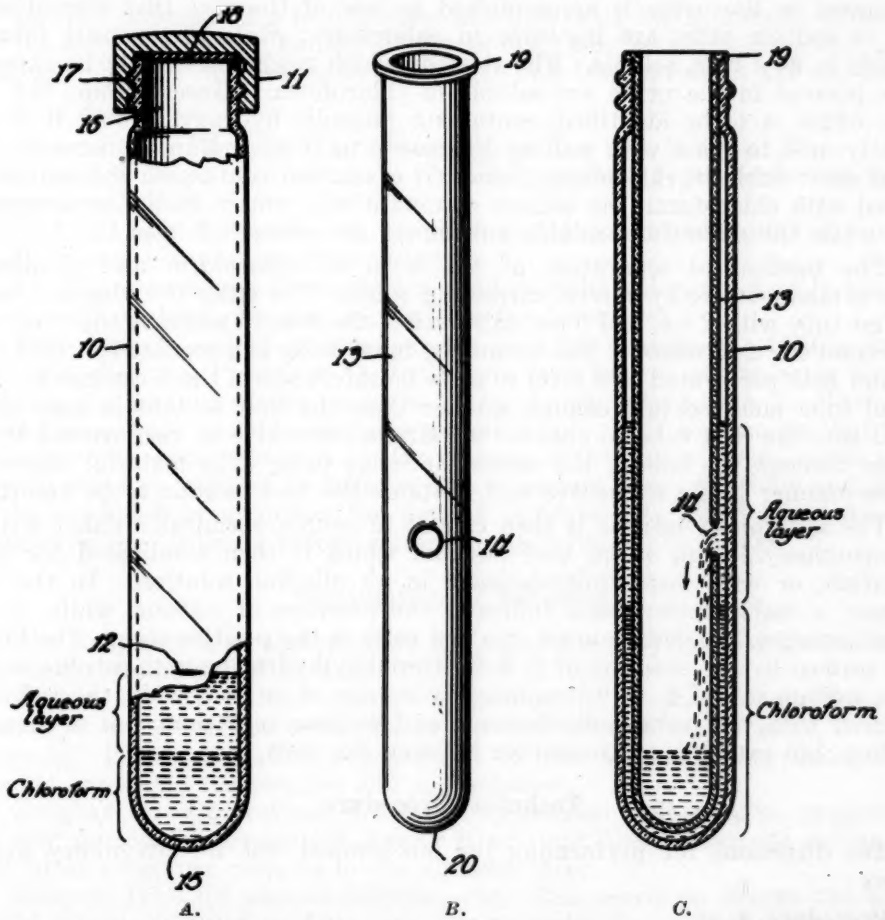

Fig. 1.—*A*, Shows the outer tube, with the aqueous and chloroform layers in place. *B*, Shows the inner tube. Item 14 is the hole through which the aqueous layer flows when the two tubes are put together. *C*, Shows the two tubes together. Note that the aqueous layer, being the upper stratum, flows through the hole, while the chloroform layer remains in the outer tube.

Principles of Biochemical Test

The biochemical test presented in this paper is concerned with the identification of free estrone in the amount present in pregnancy. The reagents are standardized so that they do not recognize the lesser amount which may be found at certain cyclic intervals in the nonpregnant individual. The test is performed in two test tubes (Fig. 1). One is a standard screw-cap test tube. The diam-

eter of the other tube permits it to fit within the first tube, but contains a perforation at a proper level to permit the withdrawal of an upper stratum of the fluid which separates as a result of the extraction process to be described. This layer contains the estrone extractive to be identified by the 2, 4-dinitrophenylhydrazine.

Mechanism of Test.—The test depends upon the presence of a substantial amount of free estrone in the urine of pregnant women. Since female urine contains progesterone in substantial amounts at certain menstrual phases, for purposes of identifying a pregnancy test it is necessary that the estrone and progesterone be separated, thus assuring that progesterone is absent from the solution to be tested for the reaction with the color-producing reagent.

This separation of estrone from progesterone and other possible interfering substances in the urine is accomplished by use of the fact that steroid salts, such as sodium salts, are insoluble in chloroform, while the nonsalt form of steroids is, as a rule, soluble. The steroids which might reasonably be expected to be present in the urine are soluble in chloroform. Since estrone, the hormone which is to be identified, contains a phenolic hydroxyl group, it is sufficiently acid to react with sodium hydroxide to form sodium estronate. This salt is not soluble in chloroform; hence, if a solution containing this salt is extracted with chloroform, the sodium estronate will remain in the aqueous solution, while the chloroform-soluble substances are extracted from it.

The mechanical separation of the layer of chloroform and alkalinized urine is made simple by special extracting tubes. The outer chamber is a screw cap test tube with 2 c.c. and 5 c.c. calibration, the first to measure the urine and the second the chloroform. The second, or inner tube, is a regular test tube with a round hole perforated at a level so as to be safely above the 5 c.c. mark. This second tube must be just enough smaller than the first so that it may be inserted into the first tube to enable the estrone extractive to rise around it and to flow through the hole of the second or inner tube. The material drawn off in this manner is the extractive and contains the free estrone to be identified.

The solution of estrone is then caused to couple chemically either with 2, 4-dinitrophenyldiazine in an acid medium which is then alkalinized for color formation, or with meta-dinitrobenzene in an alkaline solution. In the first instance, a stable brown color indicates the presence of estrone, while, in the second instance, the development of a red color is the positive sign. The brown color formed by the coupling of 2, 4-dinitrophenylhydrazine with estrone is that of the sodium salt of 2, 4-dinitrophenylhydrazone of estrone, while the red color produced with the meta-dinitrobenzene and estrone represents not a chemical coupling, but rather a color complex between the two.

Technical Procedure

The directions for performing the biochemical test for pregnancy are as follows:

Procedure A.—

1. Place 2 ml. of urine in the outer chamber or tube of the extraction apparatus.
2. Add 2 drops of Reagent I (0.5 normal sodium hydroxide) and mix well.
3. Add Reagent II (chloroform, U.S.P.) up to the second mark on the extraction chamber.
4. Close the chamber with the screw cap and shake vigorously for at least 30 seconds.
5. Allow to stand quietly until the two layers have separated sharply (about 1 minute).

6. Remove the screw cap and insert the inner tube of the extraction apparatus slowly into the outer chamber until the tube is completely inserted. Care should be exercised not to mix the layers, as only the upper, clear stratum is desired for testing.

7. Separate the two tubes and discard the solution in the outer chamber. Rinse this with water and pour contents of inner tube into the outer extraction chamber.

8. Add 4 drops of Reagent III (0.5 normal sulfuric acid) and mix well.

9. Add 5 drops of Reagent IV (saturated 2, 4-dinitrophenylhydrazine in 70 per cent ethanol). This solution must not be more than 24 hours old. Mix well, and allow to stand 10 to 15 minutes to permit complete coupling of reagent with free estrone.

10. Add 2 c.c. of Reagent I, mix well, and observe.

11. The presence of a brown color which persists for 2 minutes or more is positive for pregnancy. Fading of the brown color to the usual clear amber urine color or to a colorless state is negative and free estrone is not present.

Procedure B.—

Proceed as in Procedure A, through Steps 1, 2, 3, 4, 5, 6, and 7.

8. Add 5 drops of Reagent V (freshly prepared 1 per cent metadinitrobenzene in ethanol).

9. Add 1 ml. of Reagent VI (15 per cent potassium hydroxide) and mix.

10. Allow to stand about 10 minutes.

11. Observe colors. If there is a reddish-violet color, the test is positive; if not reddish-violet, the test is negative for pregnancy.

Procedures A and B are two separate tests for pregnancy. If it is desired to have a check on Procedure A, both tests may be run at the same time by doubling the amount of the reagents up to and including Step 7. Thereafter the end steps must be included for completion only, as it was known that metadinitrobenzene would produce a color reaction with estrone. This latter procedure, however, is subject to failures due to certain drug reactions and should not be depended upon unless the patient is advised to avoid all medications whatsoever for 48 hours before collecting the urine to be tested.

Composition of Reagents

The composition of the reagents and their functions should be understood so as to determine and correct any failure if it occurs.

Reagent I.—0.5 normal sodium hydroxide. This reagent alkalinizes the solution of urine and serves to change the free estrone in the urine to sodium estronate. It does not affect progesterone in this manner; hence this hormone does not enter into the reaction and is eliminated.

Reagent II.—Chloroform, U.S.P. This reagent will dissolve progesterone and any steroids in the nonsalt form. It will not dissolve estrone sodium salt. This latter substance remains in the aqueous layer.

Reagent III.—0.5 normal sulfuric acid. This serves to change the sodium salt of estrone to the free form and also to make the acidity optimal for the coupling reaction which follows.

Reagent IV.—Freshly prepared saturated 2, 4-dinitrophenylhydrazine in 70 per cent ethanol. This couples with estrone in acid medium to produce a complex substance, the sodium salt of 2, 4-dinitrophenylhydrazone of estrone, which will produce a brown color with alkali. To assure stability, this reagent should be prepared fresh and not used after 24 hours. The solvent is oxidized on standing.

Reagent V.—1 per cent meta-dinitrobenzene in ethanol. This reagent reacts with the characteristic linkage—$CO\text{-}CH_2$—in estrone to produce a color complex of red in the presence of alkali.

Reagent VI.—15 per cent potassium hydroxide. This solution alkalinizes the reaction mixture and develops the characteristic reddish-violet color upon which the test depends.

Only Reagents I, II, III, and IV are required for the biochemical test for pregnancy, as performed in Procedure A. Procedure B is added only for sake of comparison and is not used alone for the pregnancy test because of its potential failures. For this reason, the statistics which follow are concerned with the biochemical test as performed in Procedure A.

Comment

The present series consisted of 1,640 individual cases on which tests were performed at various months of pregnancy in order to determine the over-all accuracy and also to ascertain if there were any variable factors from month to month which would affect the accuracy; 2,560 tests were performed. In this series, 2,537 were positive, with an accuracy of 99.1 per cent. There were 23 negative reactions, giving an error of 0.9 per cent. In addition to the 1,640 pregnancies, 500 known or alleged nonpregnant individuals were tested without error. In this series, toxemia did not sufficiently lower the free estrone content of the urine to be detrimental to the test. Hypertensive patients were classified as having pre-eclampsia or threatened eclampsia, with or without albuminuria and essential hypertension. Fifty-nine patients showed albuminuria, 53 were free of albuminuria, and there were 5 cases of essential hypertension. In these 117 cases, all tests were positive. In two, the fetal heart tones were absent. Two patients were syphilitic with negative Kahn tests following treatment. Two with positive pregnancy tests had glycosuria with albuminuria and one without. Two patients showed positive pregnancy tests and were pregnant but had negative Friedman tests. Only one patient had a negative test after previously having been positive.

In two cases of hydatidiform mole the test was positive with high dilutions of urine and in two cases of chorionepithelioma the same was true. All four became negative within 10 weeks following treatment, indicating complete recovery, thus offering a good prognosis. Thus it is seen that this test may aid in the final prognosis as well as diagnosis.

Table I is a tabulation of the 1,640 cases with 2,560 tests by months of gestation.

TABLE I.

MONTH	CASES	POSITIVE	NEGATIVE
First	218	206	12
Second	574	572	2
Third	308	304	4
Fourth	181	180	1
Fifth	204	202	2
Sixth	183	183	0
Seventh	216	215	1
Eighth	291	290	1
Ninth	385	385	0
Total	2,560	2,537	23
Per cent	100	99.1	0.9

The return of the test to negative following delivery is naturally dependent upon complete removal of all placental tissue, which required but a few days. Only four patients were positive at the time of their final examinations at six weeks. In the threatened abortion cases tested, four were positive, and abortion was incomplete, while nine were negative, and dilatation and curettage failed to produce any living chorionic tissue. It would seem, therefore, that a nega-

tive test would indicate complete abortion, complete placental separation, or placental death and interference would be indicated only by hemorrhage. Four of five tubal pregnancies were positive. The reaction is positive with blood serum as well as with urine. Urine, as for other tests, should be filtered or centrifuged; blood requires centrifuging. Uterine fibroids do not produce a positive test.

How early pregnancy can be diagnosed is a moot question, as the patient presents herself for care only after the first missed period. In this series, however, there were three patients who had been undergoing sterility study. During this time they presented weekly specimens in anticipation of becoming pregnant and met with success. In these three cases, positive tests were obtained before the first missed period.

The possible causes for failure of the test present few minor difficulties that might confuse the issue. Brief consideration, however, is warranted. Ketosis from diabetes or starvation would present a different reaction, to say nothing of their individual diagnostic characteristics. Phenylpyruvic acid in the urine produces reactions unlikely to be confused. Pyruvic acid is unlikely to be present in the urine; its color curve is different and the cause may be readily determined.

For laboratory and hospital purposes, photoelectric colorimetric methods are adaptable for quantitative determination which would be of value in both direct and differential diagnosis.

Summary

In conclusion, the biochemical test for pregnancy is an office procedure, simple and economical in performance. The time required is but 20 to 30 minutes. Quantitative studies establish the early differentiation between pregnancy, hydatidiform mole, and chorionepithelioma. The time, labor, and expense involved in the use of animals in a test for pregnancy are eliminated. Errors due to animal immaturity, isolation, and sex do not occur. The reagents used in the biochemical test for pregnancy are inexpensive. Positive reactions in this test occur earlier than in any other test known. The apparatus requires only two test tubes. Valuable time is not lost in such emergencies as tubal pregnancy. The accuracy in 1,640 cases, involving 2,560 tests, has been 99.1 per cent, unquestionably a high percentage of accuracy.

I wish to acknowledge the aid of Dr. G. W. Rapp in carrying out some of these tests and in the design of the extraction tubes.

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EXFOLIATIVE DYSKARYOTIC CELLS ASSOCIATED WITH ATYPICAL CERVICAL LESIONS

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THE vaginal smear has become an accepted aid in cancer diagnosis. In some institutions, where the facilities permit, it is used routinely. It is recognized that the degree of accuracy in the interpretation of vaginal smears is variable, depending in part upon the technique utilized in obtaining the specimens, and the experience of the cytologist.

A positive smear is considered presumptive evidence of a malignant lesion, which, however, requires further confirmation by cervical biopsy and/or uterine curettage. With increasing knowledge, the percentage of false positive interpretations has steadily decreased. Yet, there is still much to be clarified in the differentiation of carcinoma cells from nonmalignant variations. In this paper an attempt will be made to evaluate the significance of dyskaryotic cells in the vaginal smear, as related to atypical cervical lesions and the development of cervical carcinoma.

The criteria used in the diagnosis of cancer by cytological study are based on the structural modifications of the individual cells, with particular emphasis on nuclear morphology. The term "dyskaryosis" has been applied by Papanicolaou[1] to those nuclear changes which are sufficiently atypical that they suggest the possibility of malignant origin. Superficial dyskaryosis refers to atypical cells derived from the outer layers of squamous epithelium. Intermediate or navicular dyskaryosis and parabasal cell dyskaryosis are applied when the abnormal cells are predominantly derived from the deeper epithelial layers.

Dyskaryotic cells have been found in conjunction with unquestionably malignant cells, in smears of carcinoma in situ, or invasive squamous-cell carcinoma. Papanicolaou has noted that in a large percentage of dyskaryotic smears further investigation by cervical biopsy proved persistently negative for carcinoma. Nevertheless, he considers the presence of dyskaryotic cells to be suggestive of an early, localized, low-grade malignancy of the cervix.

The dyskaryotic cells may be characterized by such nuclear abnormalities as enlargement, hyperchromatism, multiple or double nuclei, and not infrequently by the presence of a distinct perinuclear vacuole. Some show cornification, and are clearly acidophilic (Fig. 1).

Ayre[2] refers to dyskaryotic smears as showing a "precancerous cell complex," and believes these changes to be indicative of a transitional phase between benign and malignant lesions. He has followed those patients presenting dyskaryotic smears, and claims that 6 out of 7 developed cervical cancer in 6 to 18 months.

When dyskaryotic cells are associated with obviously malignant cells, no problem is presented. On the other hand, when found alone, how shall they

be regarded? Should further smears and biopsies be taken? Is the dyskaryotic smear an expression of a significant cervical lesion? What does the future hold in store for these patients? The answers to these questions are of importance, and will probably be found in exhaustive study, careful correlation with biopsied or resected specimens, and by observation over long periods of time.

Present Study

In 2,000 cases studied by vaginal smears, there were 12 instances in which a dyskaryotic type smear was found. These were not in conjunction with carcinoma. The cervices in these cases were then biopsied one or more times. Microscopic examination revealed a uniform lesion. All the biopsies presented an atypical picture, characterized by varying degrees of cellular proliferation, anaplasia, cell atypism, basal-cell hyperactivity with intact basement membrane, and occasional mitoses (Fig. 2). Basal-cell proliferation was usually slight and did not involve the entire thickness of this layer. Cellular stratification was disrupted in some cases, but not completely lost. The minimal criteria necessary for the diagnosis of an intraepithelial carcinoma were not present,[3] nor was invasiveness noted. Yet, the histologic changes were definitely beyond the variations of normal.

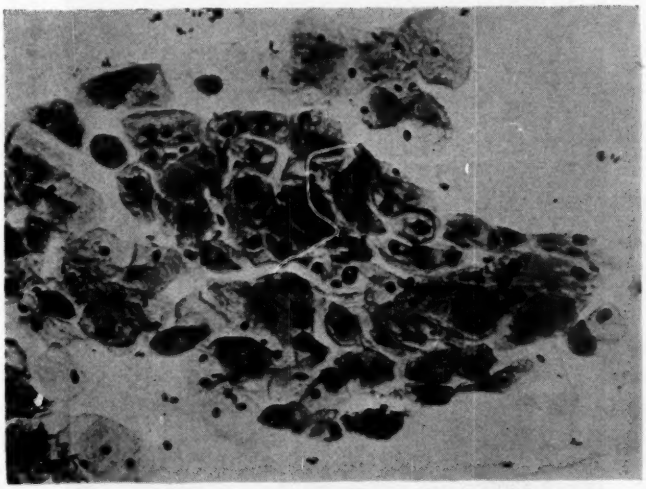

Fig. 1.—Photomicrograph of superficial dyskaryotic cells. These cells are characterized by such nuclear abnormalities as enlargement, hyperchromatism, multiple nuclei, and not infrequently by the presence of a distinct perinuclear vacuole.

The 12 cases of cervical atypism manifesting a dyskaryotic smear were carefully followed by repeated vaginal smears and cervical biopsies over a period of 9 months to 4 years. In one instance, in which the original cervical biopsy had been reported as showing markedly increased cellular proliferation without mitosis, a positive smear was found 2 years later. Cervical biopsy at this time revealed an immature squamous-cell carcinoma. In 2 other cases, the original dyskaryotic smears were associated with biopsies revealing hyperchromatic basal cells, and cellular atypism with mitosis. In the course of 1½ years these findings proved reversible*; repeated smears and biopsies being

*Papanicolaou[4] has made a similar observation, Younge, Hertig, and Armstrong[5] have reported 4 cases in which positive vaginal smears were associated with biopsies showing "only the minimal criteria (for carcinoma in situ), i.e., surface differentiation. At this stage the disease may be reversible."

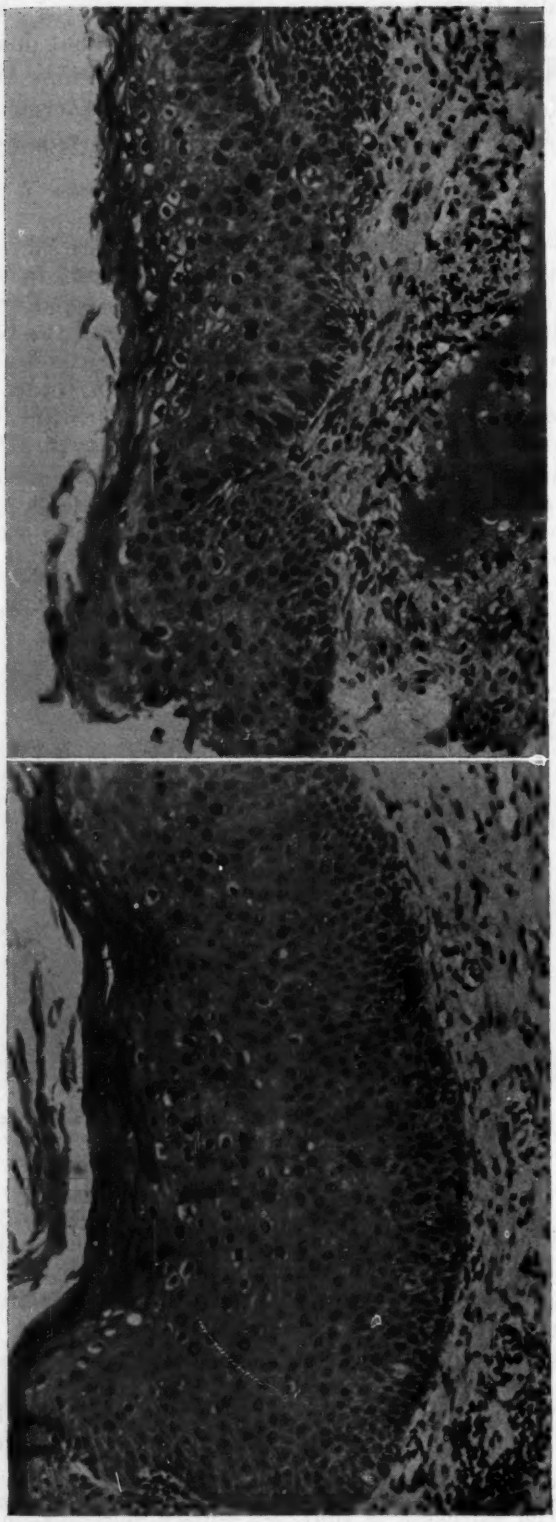

Fig. 2.—Photomicrograph of cervical biopsy. The atypical histological changes are characterized by varying degrees of anaplasia, cell atypism, occasional mitoses, and some basal-cell hyperactivity. The basement membrane is always intact.

normal. In the remaining 9 cases no change was noted in subsequent smears or biopsies. Thus, 9 cases remained unchanged, 2 reversed to normal, and one progressed to an unequivocal carcinoma.

Because of the relatively short follow-up in this series, 556 consecutive cervical biopsies taken 4 to 10 years ago were re-studied. Of these 13 showed the same degree of atypism as described above. Investigation of these cases 6 to 10 years after the original biopsies revealed that 3 women died of unrelated causes, 9 had remained well, and one had developed a squamous-cell carcinoma of the cervix 6 years after her initial biopsy.

Summary

1. Cytologic study of vaginal smears has proved to be of definite value in the detection of early cervical carcinoma and carcinoma in situ.

2. Cervical dyskaryotic cells are atypical and characterized by large, hyperchromatic nuclei, often with a distinct perinuclear vacuole. The cells may be mono- or multinucleated. Some show marked cornification and are acidophilic.

3. The significance of the dyskaryotic smear is discussed. Of 2,000 consecutive cases studied by vaginal smears, 12 showed a predominance of dyskaryotic cells, an incidence of 0.06 per cent. Biopsy study of the cervix in these cases revealed the presence of "atypism" in all instances. The histologic picture included a varying degree of epithelial proliferation, anaplasia, and cell atypism with and without mitosis. The basement membrane was found always to be intact.

4. During a follow-up of 9 months to 4 years, one woman developed a squamous-cell carcinoma of the cervix, 2 years after the initial smear and biopsy. In 2 instances there was a regression to normal. The remaining 9 cases were persistently unchanged.

5. Of 556 consecutive cervical biopsies taken 4 to 10 years ago, 13 showed atypism as described above. Investigation of the present status of these patients indicated that 3 had died of unrelated causes, 9 had remained well, and one had developed a squamous-cell carcinoma of the cervix, 6 years after the initial biopsy.

6. Whether a relationship exists between the finding of a dyskaryotic smear and an atypical biopsy, and the future development of a true malignancy is speculative. The finding of an 8 per cent incidence, 2 and 6 years after the initial biopsy, is suggestive. Repeated vaginal smears and multiple cervical biopsies are most certainly indicated.

Conclusions

The exfoliation of dyskaryotic cells from the surface epithelium of the cervix, as detected by vaginal smears, occurs infrequently. The dyskaryotic-type smear is associated with an atypical histologic change in the cervix, as evidenced by biopsy. This type of cervical cell atypism was found to progress to squamous-cell carcinoma in about 8 per cent of cases (2 and 6 years after the initial cervical biopsy).

It is felt that final conclusions cannot be drawn from a study of 2,000 vaginal smears and 556 consecutive cervical biopsies. However, the findings would indicate that women manifesting dyskaryosis in vaginal smears and atypism in cervical biopsy are to be most carefully followed with repeated smears and multiple biopsies for many years to come.

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BACTERIURIA DURING PREGNANCY*

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WILLIAM ROBERTS is usually given credit for describing (in 1881) "the occurrence of micro-organism in fresh urine" and proposing the term "bacteriuria" for this phenomenon.

The presence of bacteria in catheterized urine specimens from normal pregnant women is considered by many writers separately from infection, because in numerous cases during pregnancy the bacterial invasion is at no time productive of symptoms of pyelonephritis or cystitis. The present tendency is to consider all such invasions as infections, provided contamination of the culture can be excluded. Although sterile urine is by far the commonest finding in pregnancy, bacteria are demonstrable much more frequently in the pregnant than nonpregnant. The bacterial found in the urine may represent an original invasion in the course of pregnancy, or the quiescent stage of a previous infection. It is sometimes difficult to determine, when a pregnant patient with infected urine is examined, whether the infection occurred during the present pregnancy or antedated it.

It is difficult to indicate accurately the frequency of bacterial invasion of the urine in pregnancy. Table I shows the bacterial findings in urine of pregnant patients observed by several investigators. It may be noted that there is considerable variation in their findings.

TABLE I. BACTERIAL FINDINGS IN URINE OF PREGNANT PATIENTS OBSERVED BY VARIOUS INVESTIGATORS

AUTHOR	DATE	NUMBER OF PATIENTS	PER CENT POSITIVE URINES	REMARKS
Englehorn	1908	56	60	
Crabtree and Prather	1930	192	13	Mostly primiparas
Dodds	1931	360	11	Pregnant women 7.5% *B. coli* 3.5% other organisms
Reed	1931-32		15	
			26	Two studies
Baird	1936	390	37.7	Primiparas
			34.5	Multiparas
Hundley, Siegal, Hachtel, Dumler	1938	50	78	Up to sixteenth week of pregnancy

We consider bacteriuria as an infection since there is evidence that it plays a role in postpartum urinary-tract infection. This is especially evident in cases associated with urinary retention, and particularly in the presence of kidney

*Presented at a meeting of the Philadelphia Obstetrical Society, Oct. 5, 1950.

damage. Baird demonstrated that the majority of pregnant women showed these invasions to be present after the fourth month, and that few acquire them after the eighth month of gestation. These invasions do not always result in the production of pus, and in many cases they do not even produce symptoms at any time during pregnancy. Crabtree and Prather (1930) found that only 2 of 32 women with bacteriuria in a series of 200 cases developed pyelonephritis. Gustafsson (1916) observed that 87 per cent of his cases with both bacteriuria and pyuria failed to develop symptoms.

We think it is of interest to mention that the time of onset of infection shows that the peak incidence for primiparas is the fourth and fifth months while for multiparas it appears earlier in pregnancy. This latter group consists chiefly of those patients who had previous urinary infections, antedating the pregnancy.

Primiparas are much more likely to become infected than are multiparas. According to Crabtree, "There is a definite relationship between the time of incidence and the time in pregnancy in which the greatest degree of atony and stasis in the urinary channels is produced. This relationship is different in primiparae and in multiparae. It has been shown that the maximum degree of pregnancy urinary changes, that is the greatest degree of atony and stasis, is present in the fifth to the seventh months, inclusive. Primiparae show greater degrees of change than do multiparae and it appears earlier. A large number of multiparous patients infected from previous pregnancies show infection early in pregnancy, so that manifestations may be expected at any time in those who have already borne one child or had an infection. However, in normal primiparas there is little likelihood that infection will make its appearance before the fourth or fifth month."

Bacteriologic Studies

The patients included in this study were selected at random from those attending the maternity outpatient department of the Jefferson Medical College Hospital. These women received the regular prenatal care and studies that all patients attending this clinic receive. In addition special bacteriologic studies were carried out. The number of patients included in this study totaled 48.

The bacteria reported in this paper were isolated from catheterized urine specimens obtained under aseptic and antiseptic conditions. The urine was centrifuged and the sediment streaked on plates containing blood infusion agar, desoxycholate agar, and nutrient agar. In addition to the qualitative bacterial studies, bacterial counts of the organisms present were determined by using the pour plate method.

TABLE II. RESULTS OF BACTERIOLOGIC STUDIES OF URINE IN 48 PREGNANT WOMEN

ORGANISM	NO. OF CASES IN WHICH IT WAS FOUND	%
Streptococci		
Alpha hemolytic	2	
Beta hemolytic	2	18.1
Staphylococcus aureus	9	40.8
Coliform	9	40.8

Forty-five and eight-tenths per cent of the patients showed bacteria in urine.

Results: In our studies we found that 45.8 per cent of the patients observed showed bacteria in the urine. Seven patients were morbid post partum with symptoms referable to the urinary tract. Therefore, 31 per cent of those showing bacteriuria during pregnancy were morbid.

Fig. 1 represents the distribution of the various age groups. It may be noted that 40 of the patients studied fell within the group from 14 to 30 years old, and 34 of the patients studied were between 14 and 25 years of age. It is easy to understand this distribution since the age groups mentioned correspond to the childbearing period.

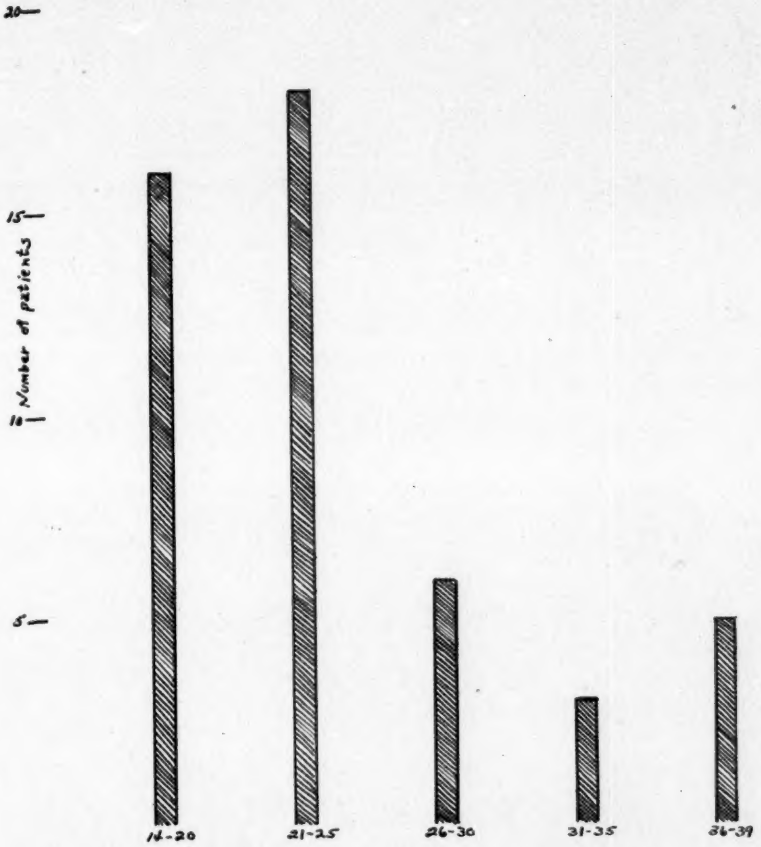

Fig. 1.—Distribution according to age groups of 48 pregnant patients studied.

Table III presents the various complications found during pregnancy in the patients studied. Although we do not feel that the diseases complicating pregnancy have a direct bearing on the urinary findings, nevertheless it is conceivable that some lesions might have an indirect influence, e.g., fibroid uterus complicating pregnancy.

In summary, 48 pregnant women were selected at random and subjected to special urinary bacteriologic studies. In our series of 48 patients, 18 were primigravidas and 30 multigravidas. It is interesting to note that of the positive urine specimens 54.5 per cent occurred in the primigravida group as compared with 44.5 per cent in multigravidas.

It was found upon examination that 22 patients, or 45.8 per cent of the total number investigated, showed bacteria in the urine. It should be remembered that all necessary precautions to eliminate contamination were observed. In Table II the types of organisms recovered on bacteriologic study and percentages were demonstrated. The entire group of patients included in this study were followed to the termination of pregnancy and throughout the puerperium. It was found that 7 patients in this entire group were morbid, but not one patient studied who had negative urine culture during pregnancy was morbid as a reesult of urinary-tract infection. The 7 morbid patients all showed bacteria in the urine during pregnancy. It can therefore be stated that 31.8 per

Fig. 2.—Distribution of patients according to gravidity.

cent of the patients who showed bacteria in the urine during pregnancy were morbid during the puerperium and furthermore the symptoms in this group were referable to the urinary tract. Urinary studies were carried out during the puerperium in these patients and the findings demonstrated bacteria and pus cells. All urines were catheterized specimens. It is of the greatest importance that all patients who showed evidence of bacteriuria during pregnancy or who were morbid during the puerperium with symptoms referable to the urinary tract should be kept under future supervision and carefully studied following their discharge from the hospital. Periodic examinations should be performed and repeated urine cultures carried out. It should be remembered that while these patients become asymptomatic, it is not proof that the infection in the urinary tract has been eradicated.

TABLE III. CONDITIONS COMPLICATING PREGNANCY IN 48 PATIENTS

COMPLICATIONS	NUMBER OF CASES
Secondary anemia	16
Gonorrhea	1
Pre-eclampsia	6
Syphilis	8
Vaginal discharge (nonspecific)	9
Cervicitis	6
Anal fissure	1
Infected tonsils	1
Hyperemesis gravidarum	1
Dysuria	1
Vincent's infection (vagina)	1
Pin worms	1
Granuloma inguinale	1
Moniliasis	1
Trichomonas vaginalis vaginitis	1
Fibroid	1

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Discussion

DR. BENJAMIN LEFF.—The high incidence of bacteriuria during pregnancy as shown in this report is indeed surprising. A control study of nonpregnant women in a similar age group would be of considerable value and interest.

DR. THADDEUS L. MONTGOMERY.—There is not much of a controversial nature in this presentation which requires extended discussion. The relatively high percentage of cases in which Dr. Bernstine has encountered bacteriuria and later evidences of urinary-tract infection again call to the attention of the obstetrician the importance of careful observation of the urinary tract during his obstetric care of the maternity patient. The close relationship of the urinary tract to the reproductive tract anatomically, embryologically, and physiologically is re-emphasized.

The responsibilities of the obstetrician are therefore clear. He must make sure whether or not his patient is entering pregnancy with a residual urinary-tract infection, whether she develops a urinary-tract infection during the course of pregnancy, and finally whether she is left with a urinary-tract infection at the conclusion of delivery. It is necessary, therefore, always to secure a catheterized specimen of urine at the first prenatal visit, repeat the catheterization if urinary-tract symptoms appear, and always secure a catheterized specimen of urine at the conclusion of the puerperium or at the first postnatal visit.

If urinary-tract infection is encountered it must be treated as specifically and completely as possible during pregnancy. If there is residual infection which requires further urologic therapy following delivery, this must be carefully attended to so that the patient is not left with a chronic urinary-tract infection the remainder of her life.

It is probable that at no other time in her medical history is a woman more susceptible to urinary-tract disease than she is during pregnancy, and much rests upon the obstetrician to keep this fact in mind.

As to some of the individual observations recorded in this presentation of Dr. Bernstine's, one wonders as to the significance of the bacteriuria itself and whether an occasional bacteriuria can occur during pregnancy without having the significance of a true urinary-tract infection. If it has not been done I think it would be wise to check all such cultures with stained urinary sediment because the chance of contamination in culture is, of course, very considerable. I presume, however, that in all such cases it is better to conclude that a urinary-tract infection is present and treat it accordingly than to consider it otherwise.

It is not clearly stated in this paper whether the infection which ultimately manifested itself during the puerperium was attributable to the same organism that was found in the bacteriuria of pregnancy. If not clearly recorded this is certainly an important point to watch in the future.

The continued observation of a large group of puerperal patients who have had urinary-tract infections should bring to light many interesting data on this entire subject matter, and Dr. Bernstine should be encouraged to pursue these investigations further.

DR. BERNSTINE (Closing).—To answer Dr. Leff's question, I am unable to give exact figures as to the number of nonpregnant women who have bacteriuria. The significance of bacteriuria is to recognize it as an infection, since pregnancy or trauma will set off the symptoms. Although we found 18 per cent streptococci bacteriuria during pregnancy, it does not follow that during the postpartum period the same percentage of streptococci will be recovered, should frank infection occur, since the streptococci are at times overgrown by other organisms, especially the *B. coli.* I would like to suggest that the taking of cultures early and the use of proper media might aid in the recovery of a greater number of streptococci from the urine.

BOUGIE INDUCTION OF LABOR*

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THE first recorded induction of labor in modern times was in 1738 in England when a midwife ruptured the membranes prematurely in a patient with a contracted pelvis. From that time until cesarean section became a relatively safe procedure, the most common indication for induction of labor was cephalopelvic disproportion before term. Since then the many methods used for this procedure have been indicative of the experimentation utilized during the past two hundred years. In the early nineteenth century Kluge inserted sponge tents into the cervix. Simpson and Scanzoni injected carbonic acid into the uterus. Krause in 1855 reported the method, now known by his name, of inserting soft rubber bougies between the membranes and the uterine wall. Kiwish used alternately hot and cold douches. The deRibe's bag, later modified by Barnes and Voorhees, was devised in 1888. This was replaced in 1925 by a sheep bladder filled with glycerine after insertion into the cervix. Baum[1] believed that the advantage was in the gradual increase in size of the bladder which occurred by osmosis. Klein,[2] in 1926, developed a procteurynter with 60 per cent success in a series of 800 cases. The method of injecting various electrolyte solutions, usually isotonic sodium chloride, into the amniotic cavity is still being used in several South American countries.[3] In England today the Drew Smythe catheter,[4] first introduced in 1937, appears to be the method of choice in most of the larger clinics.[5]

Since the turn of the century in the United States artificial rupture of the membranes to induce premature labor has been the most widely used, though many writers will admit that in selected cases both bag and bougie are of some value. The literature, however, is scant, and because indications differ as to which method is to be chosen, no true comparison has ever been reported. In more recent years there has been a tendency on the part of the profession to utilize cesarean section for the termination of pregnancy prematurely.

Material

The purpose of this paper is to review the cases of bougie induction at Cooper Hospital in the past 9 years in an attempt to evaluate this procedure in present-day obstetrics. The study includes the consecutive cases from January, 1940, to December, 1948. From Table I it can be seen that the incidence of induction by this method has been 3.3 per 1,000 live births. In no cases of eclampsia was labor thus induced. The number of cases of other toxemias are listed so that a relation can be shown, most of the indications falling in this category. The maternal mortality during this period was 1.77 per 1,000 mothers delivered. The fetal mortality was 3.87 per cent of the number of babies delivered.

*Presented at a meeting of the Philadelphia Obstetrical Society, Nov. 2, 1950.

Method

Since Krause first introduced his bougie there have been many modifications of the procedure. Fitzgerald,[6] reporting on 10 cases used a 30-inch soft rubber stomach tube, No. 24 F., sealing off the end so as to make it blind. This was inserted in its entirety into the uterus so that it coiled around the lower uterine segment. Eastman[7] believed this to be a disadvantage because of the kinking which at times caused painful tetanic contractions which are not true labor pains. He advises x-ray checks if this is ever suspected so that the position can be corrected. Laubscher[8] in using this soft tube reported difficulty in getting it past the fetal head. Thomason[9] preferred two to three smaller tubes, No. 12 F.

We have used what Morton[10] called a Wales bougie. This is a large 1.5 cm. hard-rubber rectal tube with a small lumen. It is stiff enough to obviate the use of a stylet and soft enough to be able to adapt to the lower uterine segment. With aseptic technique a finger is placed into the cervical canal to reach the membranes. (Should they rupture unexpectedly the tube is withdrawn.) After insertion for a distance of about 15 cm. iodoform gauze is packed in and about the cervix and in the vagina so as to keep the tube in place. At the end of 24 hours, if the patient is not in labor, the packing and tube are removed; if labor becomes established before this time has elapsed, removal is then performed. We have not found it necessary, as advised by Hill,[11] to use a speculum and cervical tenaculum in order to carry out the procedure under vision.

It has been shown that with a bougie in the uterus for over 24 hours local infection is invariably present, and so, when difficulty or complication is anticipated, penicillin is used prophylactically. When haste is not essential, primiparas with long tightly closed cervices usually receive one or two medical inductions with Pitocin prior to the surgical procedure, and this nearly always conditions the cervix so that entrance can be made without injury.

Analysis

The indications for induction in this series were as follows:

Pre-eclampsia, mild	25
Pre-eclampsia, severe	11
Hypertensive vascular disease, mild benign	7
Hypertensive vascular disease, severe	11
Renal Disease	
Glomerulonephritis	3
Pyelitis, chronic	1
Toxemia unclassified	
Hyperthyroidism	1
Diabetes mellitus	3
Acute psychosis	1
Intrauterine fetal death	1
Malnutrition	1
Convenience at term	3
Total	68

We no longer believe that this method should be used for convenience at term. Rupture of the membranes has been shown to be the method of choice in such cases.

The cases according to length of gestation occurred as in Table II.

The average time from induction to onset of labor in primiparas was 23.4 hours; in multiparas 18.9 hours. The average labor in primiparas was 15.6 hours; in multiparas 7.1 hours.

TABLE I. COMPARATIVE STATISTICS

	1940	1941	1942	1943	1944	1945	1946	1947	1948	TOTAL
Mothers delivered	1,565	1,704	1,926	2,265	2,478	2,477	2,686	2,887	2,986	20,974
Total live births	1,547	1,684	1,910	2,250	2,433	2,454	2,658	2,855	2,950	20,741
Toxemia excluding eclampsia	43	61	61	70	41	47	54	110	133	620
Maternal mortality	1	3	5	10	5	3	3	6	1	37
Fetal mortality	68	55	81	90	103	92	87	117	119	812
Neonatal mortality	30	21	38	50	44	39	29	62	58	
Stillbirths	38	34	43	40	59	53	58	55	61	
Bougie inductions	7	10	7	2	5	6	6	10	15	68
Maternal mortality										0
Fetal mortality	0	2	1	1	1	1	0	0	4	10
Neonatal mortality	0	2	1	0	0	1	0	0	1	5
Stillbirths	0	0	0	1	1	0	0	0	3	5

TABLE II

	WEEKS 30-32	WEEKS 33-35	WEEKS 36-39	WEEKS 40 AND OVER
Primiparas	3	4	37	7
Multiparas	2	3	8	4

TABLE III. TIME OF LABOR AND TIME TO ONSET

	LABOR (HOURS)				TIME TO ONSET (HOURS)				
	12	12-24	24-36	36-48	24	34-36	36-48	48-60	60-72
Primiparas	27	14	7	3	24	12	10	2	2
Multiparas	15	1	1	0	11	2	1	2	1

There was one failure in the 68 cases, and this patient delivered spontaneously 5 days later with no complications. This is an incidence of success of 98.5 per cent. Though the series is small it compares favorably with Morton's report[10] on 160 cases with 82.5 per cent success, and that of Gatewood and Torpin,[12] who report 95.1 per cent success in 292 cases.

We have further broken down the period of labor and time to onset according to the weeks of gestation in primiparas and multiparas as shown in Table IV.

TABLE IV

	GESTATION UNDER 36 WEEKS (HOURS)	GESTATION 36 WEEKS AND OVER (HOURS)	TOTAL (HOURS)
Average Labor.—			
Primiparas	18.1	17.4	15.6
Multiparas	8.0	6.6	7.1
Average Time to Onset.—			
Primiparas	21.5	23.7	23.4
Multiparas	34.2	12.2	18.9

The 12 cases of less than 36 weeks' gestation are evenly divided between primiparas and multiparas. This trend of greater difficulty in inducing multiparas in the early periods of gestation has been noted by others,[11, 13, 14] and it is felt that this is definitely a hazard in utilizing artificial rupture of the membranes as a method of induction.

In reviewing the types of delivery, we find there was a forceps incidence of 43 per cent in contrast to an over-all forceps incidence over the 8-year period of 20 per cent. We are more aware that after surgical induction the second stage should not be unduly prolonged. This is so because of the slightly longer and harder first stage of labor with the concomitant dangers of inertia, infection, morbidity, and fetal mortality.

TABLE V. TYPES OF DELIVERY

Spontaneous vertex	34
Low forceps	29
Midforceps	2
Breech	3
	68

There were 5 cases of persistent occiput posterior, 3 cases of transverse arrest, and 1 face presentation. Since complications of position and presentation are more common, all cases of surgical induction should be under the most expert supervision available.

The postpartum period can be summed up as follows:

Normal puerperium with recovery	45
Persistent hypertension	15
Persistent nephritis	3
Persistent diabetes	3
Persistent psychosis	1
Persistent hyperthyroidism	1
Maternal mortality	0
Maternal morbidity	5 (7.3%)
Fetal mortality	10 (14.7%)

Of the 5 morbid cases, 3 were due to endometritis which subsided spontaneously; 1 was a case of postpartum convulsions which we could not attribute to the induction since the patient was in an advanced state of malnutrition, anemia, and nephritis; the fifth was due to puerperal sepsis in a patient with nephritis prior to interference.

At first glance the fetal mortality is quite high, but on analysis there was one case following intrauterine death. Another was a case of 30 weeks' gestation with acute nephritis. Three babies were 32-week premature infants from toxic mothers. Two were 34-week infants following nephritis and severe preeclampsia, respectively. There was one case of diabetes mellitus uncontrollable at 38 weeks; and last, a toxic postmature elderly primipara for which condition no good cause could be determined.

Comment

In a review of the literature on induction of labor few adequate comparative studies could be found. This is somewhat surprising since the decision, calling for some experience and always approached with considerable deliberation, is a subject of keen interest to every obstetrician. It is true that before cesarean section became so safe and so popular many more indications arose. As late as 1927, however, Thomason[9] in England made the following statement: "There are two schools of thought today in regard to induction of labor in cases with contracted pelvis. The first is to allow the pregnancy to go through term and labor and, if there is disproportion, sacrifice the baby but induce premature labor in subsequent pregnancies. The second is to watch the growth of the fetus in the first pregnancy and if it fixes with difficulty in the pelvis, induce the patient. The second is obviously preferred." Today no one would think of induction of labor prematurely for cephalopelvic disproportion. Where the question for deliberation lies is usually in the case of the toxic patient (whose pregnancy should be terminated to preserve the health of the mother), as to whether to rupture the membranes, use a bougie, or subject the patient to cesarean section.

About 15 years ago a plea was made by Slemmons,[15] Guttmacher,[16] and others to utilize artificial rupture of the membranes as a method of choice. Their reports, however, deal with selected cases most of which were near

term and without complications. Indeed, Eastman[17] claimed in 1938 that the four contraindications to rupturing the membranes were (1) an unengaged head, (2) more than 10 days prior to the estimated date of confinement, (3) a long, firm cervix, and (4) breech presentation. Should, then, the large number of indications for interrupting pregnancy which fall outside these criteria call for abdominal section? There is a present-day tendency in this direction.[18, 4] Cesarean section has risen in incidence in some places to heights it has never reached before. Refinement of techniques, chemotherapy, and antibiotics have been largely responsible for this. Is it not possible that with these same agents induction of labor can be made safer to a similar degree? The danger of sepsis in the use of the bougie, always stressed,[18, 19] has not been a serious worry in our series. Corkhill[20] had no cases with reportable fevers in his group.

The objection to hemorrhage from the placental site has never been reported as a cause for fetal death or abruptio placentae. That the method is successful in only small percentage of cases is obviously false. That labor is prolonged has not been borne out in our experience or the experience of others, so long as the length of gestation is considered in comparison with both spontaneous premature labor and those induced by artificial rupture of the membranes. This comparison is frequently omitted in the literature. The protracted course following rupture of the membranes in early gestational cases, due to the long, tightly closed, unprepared cervix, especially noted in primiparas, as well as the often reported[13, 16, 17, 21, 22] increased incidence of prolapsed cord, is in the main our reason for choosing bougie induction. Before the lower uterine segment and cervix have been properly prepared physiologically for labor, intact membranes are helpful in the thinning-out process. Fetal mortality is high, but a large number of the cases dealt with will be those of toxic mothers under 36 weeks of gestation, cases which have a poor outlook for the fetus no matter what method is used, cases which many writers are prone to exclude in their dissertations on inductions of labor.

Summary

Sixty-eight cases of bougie induction of labor have been analyzed, covering a nine-year period from 1940 to 1948, inclusive.

The method is described.

The literature has been reviewed and compared with the results obtained.

In selected cases bougie induction remains a procedure of choice.

Grateful acknowledgment is made to Drs. A. B. Davis and G. B. German, under whose supervision the work was performed, to Dr. R. A. Kimbrough who assisted with the manuscript, and to Miss Mildred Leicht who helped in processing the records.

Addendum

Communication with Dr. B. F. Lovett, chief resident at Cooper Hospital, reveals that from January, 1949, to September, 1950, a total of 36 bougie inductions have been performed. The indications were all pre-eclampsia of various degrees. There was no maternal mortality. There was a maternal morbidity of 3 (8.3 per cent). There was a fetal mortality of 2 (5.5 per cent). There were 3 failures attributed to difficulty in technique. These patients delivered within 3 days of interference with no complications.

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Discussion

DR. PHILIP F. WILLIAMS.—Dr. Knerr has drawn our attention to a method which was once quite popular but with which many of the audience may be unfamiliar. Personally, I have not used the tube or bougie induction for more than ten or fifteen years. This series of inductions has been done mainly for toxemias, of which one-third were regarded as severe. It is interesting to note that, in the hospital concerned, the type of toxemias for which this method was regarded as particularly suited nearly doubled as to incidence, while the percentage of use of tube induction dropped sharply through the same years.

The philosophy of the method is the initiating of uterine contractions by the irritation of the foreign body introduced, tube, bougie, or bag. Rupture of the membranes, by many regarded as simpler and safer, makes the fetus the irritating factor.

The latent period, as given, seems long when one realizes the need for mechanical induction was more immediate. Arnold, who used this method quite often, states that he had a latent period of from one to six hours with a larger diameter solid bougie. Arnold did not regard rupture of the membranes as a contraindication to the use of his tube for induction.

One may question, not the indications, but the choice of this type of induction in the presence of severe disorders of metabolism and with the cervix long and tightly closed. The abdominal hysterotomy appears to be the present-day choice of interruption in many clinics, with hysterectomy where future conception is banned.

That the maternal mortality was zero and the fetal loss so slight is assurance that this method may be regarded as a safe method where induction is indicated without need for the speed of a section.

DR. A. B. DAVIS.—Personally, I have not done a bougie induction for ten or fifteen years. I hope you will all note that here it was not done for disproportion. It was done in cases where toxemia or threatened eclampsia was the issue. Medical induction in which Pituitrin or Pitocin is used tends to increase tension, both hypertension and the nervous tension of the patient. To eliminate these things surgical induction is employed. I tried the Arnold bougie for a while but soon discontinued it. The bougie does not curl up in the lower uterine segment, as does the rectal tube usually used. It is twice the size of the rectal tube and, I believe, dangerous to use because it is firmer and harder. I think I lost a patient on that account once. I left the bougie in more than 24 hours and it was pretty well up into the uterus. We did not have any penicillin in those days or the sulfonamides or antibiotics and the patient developed sepsis. That, of course, is another point against any surgical interference. However, now, it is much safer than it was then. If you remember that these were cases of threatened eclampsia, or definite toxemia, in which the woman with the baby out has a better chance than the woman with the baby inside, I think you will agree the results are as good as can be expected.

ACUTE ISOLATED MYOCARDITIS IN PREGNANCY

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THE incidence of myocarditis and its clinical significance are disputed. Some state it occurs with relative frequency and question its seriousness. Others consider it rare and of great importance. In former years physicians commonly made the clinical diagnosis. Gore and Saphir[1] recalled attention to this condition by reporting 35 fatal cases of myocarditis complicating acute nasopharyngitis and tonsillitis. The authors suggested the following classification of myocarditides[2]:

1. Following infectious diseases.
   (a) With endocarditis.
   (b) Without endocarditis.
2. Specific, with characteristic anatomic structure, or identifiable pathogenic organism.
3. Due to chemical poisons, physical agents, or hypersensitive states.
4. Isolated, unassociated with any known illness.

The term "isolated myocarditis" is synonomous with "isolated diffuse myocarditis," "isolated interstitial myocarditis," and "Fiedler's myocarditis." It denotes an idiopathic, nonspecific, isolated inflammatory lesion of the myocardium. It occurs at all ages about equally in both sexes but is most common in childhood and early adult life. Clinically there is progressive cardiac failure unassociated with any of the better-known causes of decompensation. A correct antemortem diagnosis is seldom made. Dyspnea is the common presenting symptom. The pulse is weak and thready and hypotension is significant. Pulse and temperature ratios are unusual with marked tachycardia and mild irregular fever. Chest pain characterized by substernal oppression is frequently described. Manifestations of congestive failure are striking. Chest films show cardiac enlargement and pulmonary congestion. Electrocardiograms usually reveal evidence of myocardial damage. Embolic phenomena are observed and unexpected deaths are numerous.

Postmortem examination shows varying degrees of cardiac hypertrophy and dilatation. The myocardium alone is involved while the pericardium, endocardium, and heart valves are not affected. Mural thrombi are frequently seen. Cases are divided into two groups: those with diffuse inflammatory myocardial lesions; and those with granulomatous lesions. Neither form is pathologically specific. In the diffuse type there is infiltration of lymphocytes, mononuclear cells, polymorphonuclear cells, eosinophilic cells, and plasma cells. Fibroblasts occur in varying quantity. Different stages of the disease process are seen,

beginning with early cellular infiltration and parenchymal involvement, and culminating in complete sarcoplasmic degeneration and extensive fibrosis.

The first clear account of this disease is attributed to Fiedler[3] in 1890, although in 1888 Steffen[4] reported two cases of myocarditis which probably were of this same type. Saphir[5] found 240 cases (4.3 per cent) of myocarditis in 5,626 autopsy cases. Fifteen were of the Fiedler variety. None of these authors mention pregnancy complicating myocarditis.

The etiology of isolated myocarditis remains obscure. Aschoff[6] suggested an infectious or toxic origin. Kaufman[7] attributed it to the toxic action of bacterial products since bacteria had never been identified. Sacks[8] believed the diffuse infiltrations represented exaggerated examples of the rheumatic fever Aschoff body but this theory has not been accepted. The granulomatous lesions were formerly attributed to tuberculosis and syphilis but neither acid-fast bacilli nor spirochetes have been identified with the lesions. The granulomatous lesions have also been attributed to a special form of hypersensitivity particularly that due to arsphenamine.[9, 10, 11, 12]

The relation of myocardial disease to pregnancy has received relatively little attention. Virchow[13] and Porak[14] mentioned myocardial degeneration in connection with puerperal deaths. As early as 1898 Vaquez and Millet[15] described what they erroneously considered as specific infectious or toxic myocardial lesions of pregnancy. Meyer-Ruegg[16] called attention to similar degenerative myocardial lesions. Blacker[17] stated that myocardial disease unaccompanied by valvular lesions was important in producing cardiac failure during and after pregnancy. Campbell[18] wrote that "myocardial disease shared the doubtful privilege with auricular fibrillation of being ranked as the most dangerous complication of pregnancy." Williams[19] claimed that 1.5 per cent of cardiac deaths during and soon after pregnancy were the result of an idiopathic myocarditis. Herrmann and King[20] reported three deaths due to pulmonary thrombosis in four patients with serious idiopathic myocardial degenerative changes. Gouley, McMillan, and Bellet[21] reported seven patients with severe puerperal failure. Four died several months following delivery. The authors emphasized the parenchymal nature of the myocardial lesions and the development of mural thrombi. Rheumatic fever, rheumatic heart disease, tuberculosis, syphilis, hypertensive disease, nephritis, hyperthyroidism, and focal infection were excluded. They intimated a specific relation of the lesion to pregnancy but added they had observed similar cases in males. They further speculated regarding the role of dietary deficiency, calcium deprivation, puerperal proteolytic enzymes, and ergot toxicity. Jensen[22] described a death six months post partum with advanced myocardial scarring. Hamilton and Thomson[23] mention a puerperal death possibly due to myocarditis.

Present Study

There have been 2,310 cardiac patients in 64,992 pregnant women at the New York Lying-In Hospital from 1932 through 1950. Two patients had recognized isolated myocarditis. Both patients died undelivered and diagnosis was made post mortem.

CASE 1.—1940. P. B., a 31-year-old Negro para 0, gravida iii, registered in the antepartum clinic in the ninth week of pregnancy. Family history revealed that her father had died of a cerebral hemorrhage. Past history indicated a series of injections for syphilis twelve years previously. The initial examination revealed normal heart and lungs. The serology was negative. There was a rectal stricture and a positive Frei test. The patient was given sulfanilamide 0.3 Gm. three times a day because of the lymphogranuloma

venereum and antisyphilitic therapy consisting of a total of 0.4 Gm. bismuth, 0.2 Gm. arsphenamine, 0.9 Gm. neoarsphenamine, and 0.18 Gm. Clorarsen. Pregnancy proceeded uneventfully until the sixth month when the patient presented herself in acute cardiac failure. She had noted increasing dyspnea for five days but there had been no recognized antecedent acute infection or toxemia. On admission the temperature was 36.8° C., pulse 130, respirations 40, and blood pressure 70/40. An electrocardiogram revealed evidence of myocardial damage. Other laboratory data were not obtained as the patient died in pulmonary edema within one hour after admission. Earlier studies in the clinic had revealed a hemoglobin of 90 per cent, white blood count of 5,000, and normal urine. Arsenical encephalitis was given as the clinical cause of death.

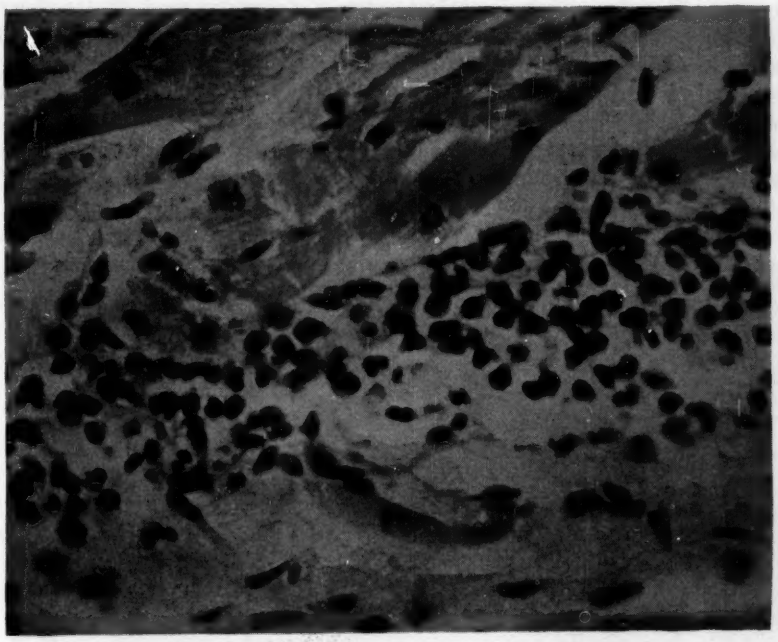

Fig. 1.—Patient P. B. There are interstitial edema and cellular infiltration consisting of monocytes, polymorphonuclear leucocytes, and plasma cells. The muscle fibers show nuclear swelling and sarcoplasmic degeneration.

Postmortem examination revealed the following: The heart was slightly enlarged, weighing 450 grams. The muscle quality was flabby. The valves were intact. The myocardium of the left ventricle was 15 mm. thick, that of the right ventricle 4 mm. thick. The papillary muscles showed faint yellow mottling. The coronary orifices were normal, the vessels patent and the walls smooth. The aorta and pulmonary artery were normal. Microscopic examination revealed the majority of muscle fibers in a poor state of preservation separated by an infiltration of monocytes and polymorphonuclear leucocytes. The muscle fibers showed nuclear swelling and sarcoplasmic degeneration. Fat stains indicated a diffuse degeneration. A section of the right auricle showed a thrombus without organization. In addition to the cardiac findings there was fatty degeneration of the liver with periportal lymphocytic infiltration, and fatty degeneration of the renal convoluted tubules. Sections of the brain were essentially normal. Small thrombi were found in the vessels of the lungs and kidneys. Culture of the heart's blood was sterile. Intracerebral mouse inoculations with extracts of the liver and spleen did not affect the animals. Accessory autopsy findings included slight bronchopneumonia, lymphogranuloma venereum of the rectum, and a six months gravid uterus with small fibromyomas. Sections of the fetal heart and kidneys were normal. Fig. 1 shows the typical myocardial lesion.

CASE 2.—1950. B. F., a 33-year-old white primigravida registered in the antepartum clinic in the eighth week of pregnancy. The family history and past history were noncontributory. The initial findings were entirely normal. No murmurs were heard and routine chest film showed a normal-sized heart. The antepartum course continued unremarkable until the thirty-first week when the patient reported in congestive failure. She had noted shortness of breath and substernal pain for three days. There had been no recognizable antecedent acute infection or toxemia. On admission the temperature was 37° C., pulse 150, and respirations 40. The patient was orthopneic and cyanotic. A systolic murmur was heard over the entire precordium and râles were present throughout both lung fields. A chest plate showed marked cardiac enlargement and pulmonary congestion. The electrocardiogram revealed evidence of myocardial damage. The hemoglobin was 90 per cent, white blood count 13,400, differential count, 76 polymorphonuclear leucocytes, 2 monocytes, and 22 lymphocytes. The urine was normal. The history of substernal pain suggested a coronary occlusion. The patient received digitalis, mercurials, penicillin, streptomycin, aminophylline, oxygen, alternating tourniquets to the extremities, and a phlebotomy. Concentrated glucose was given intravenously to combat the marked persistent hypotension, the systolic pressure averaging about 80-90. The course was progressively downhill despite all therapeutic measures and the patient died three days following admission, the temperature rising to 40.3° C. on the final day.

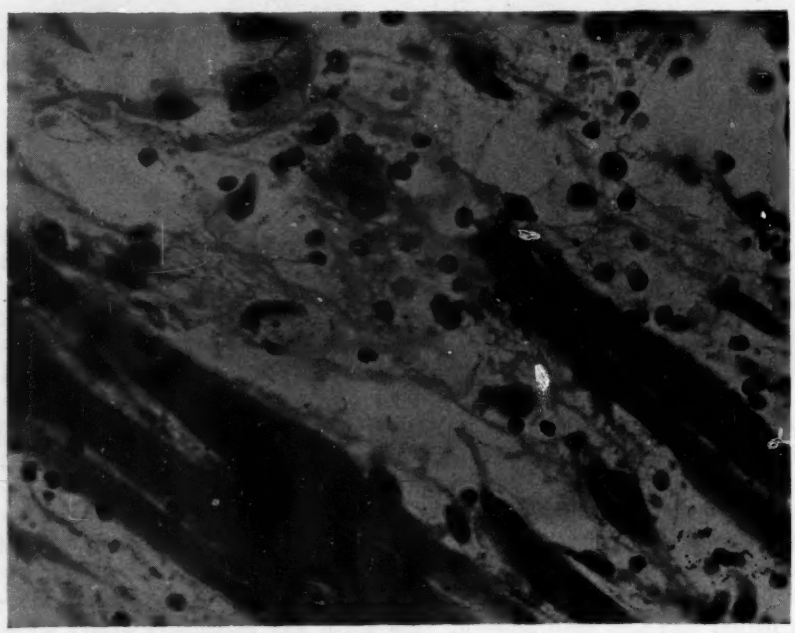

Fig. 2.—Patient B. F. There are interstitial edema and cellular infiltration consisting largely of mononuclear cells. The muscle fibers show evidence of dissolution and nuclear degeneration.

Postmortem examination revealed the following significant findings: The heart was enlarged, weighing 470 grams. The pericardial cavity contained 40 c.c. of serous fluid. The pulmonary artery and aorta were normal. The valvular structures were normal except for slight fusion of one of the commissures of the aortic valve. There were small areas of hemorrhage in the wall of the left ventricle. The orifices of the coronary vessels were not constricted and the arteries were patent without evidence of atherosclerosis. Microscopic examination showed a diffuse and focal infiltration of the myocardium with polymorphonuclear leucocytes and mononuclear cells. Focal necrosis of muscle fibers was evident with

sarcoplasmic degeneration and vacuolization. Interstitial edema was marked. The lung sections showed a slight bronchopneumonia. The uterus contained a seven months' fetus. The remainder of the examination including complete neurologic study was unremarkable. Cultures of the heart's blood and lungs were sterile. Sections from the fetus showed no abnormality. Fig. 2 shows the typical myocardial lesion described above.

Comment

These two patients presented the clinical and pathological picture of an acute isolated myocarditis. Both developed sudden congestive cardiac failure in the absence of any previously recognizable heart disease. Dyspnea and tachycardia were marked while temperature elevation was for the most part mild. Hypotension was significant. Electrocardiograms revealed evidence suggestive of myocardial damage. In neither case was a correct antemortem diagnosis made. Arsenical encephalitis was suspected in the first case. Substernal pain suggested coronary occlusion in the second. Sections of the myocardium revealed similar early interstitial and parenchymal lesions. Had the patients survived longer it is likely that further necrosis and scarring would have been evident as reported in the puerperal deaths. The pericardium, endocardium, and valves were not affected.

The physiologic circulatory burden of pregnancy was about at its peak in both patients and hydremia undoubtedly added a significant load to the involved myocardium. Had the illness developed earlier or later in pregnancy the therapeutic measures employed might have met with success. The hypotension may be correlated with the myocardial damage and the use of intravenous fluids to raise the pressure may actually aggravate the underlying pathology.

Cardiac decompensation without common etiological factors should lead one to suspect isolated myocarditis. These cases are probably quite rare unless one postulates the occurrence of mild unrecognized involvement with spontaneous cure. Patients have frequently been studied in the antepartum cardiac clinic because of dyspnea not associated with recognizable organic heart disease, yet their electrocardiograms have not been revealing, and none has developed cardiac difficulty during pregnancy or the puerperium. Autopsy studies in other maternal deaths including patients with organic heart disease have not uncovered additional instances of myocarditis. Gouley, McMillan, and Bellet[21] concluded that the term "Fiedler's myocarditis" was little more than a convenient name for myocardial inflammations that do not fall into a standard classification. Whether the picture described represents one particular disease such as an unrecognized virus infection, or a group of diseases, remains obscure. Whereas this study fails to impart positive information regarding the etiology of this condition, several negative observations can be made. Penicillin and streptomycin administered in the second case did not significantly alter its course. The first case was treated before antibiotics were available. Since both patients died undelivered neither ergot nor puerperal proteolytic enzymes need be considered. The myocardial changes described are not specific. There was no evidence of hypertensive disease, nephritis, hyperthyroidism, tuberculosis, rheumatic fever, rheumatic heart disease, dietary insufficiency, toxemia of pregnancy, or acute antecedent infection. In the first case there was long-standing lymphogranuloma venereum with rectal involvement. Despite a past history of syphilis the serology was negative and there was no evidence of this disease. The second case had no demonstrable source of focal infection. Arsenical therapy was administered in the case with a syphilitic history according to the obstetric antisyphilitic regimen of the times, yet the myocardial lesions were diffuse rather

than granulomatous as described in connection with hypersensitivity to this drug. Blood cultures were sterile and animal inoculations with tissue extracts produced negative results. The fetal organs were not affected.

Summary

Two antepartum deaths from acute isolated myocarditis are reported. These cases represent the experience with this disease in 2,310 cardiac patients out of 64,992 pregnant women at the New York Lying-In Hospital from 1932 through 1950. The literature is reviewed and the clinical and pathological features are discussed.

Conclusions

1. Cardiac decompensation without common etiological factors should lead one to suspect isolated myocarditis.

2. A history of substernal pain may confuse the diagnosis with coronary occlusion.

3. Whereas this study fails to impart positive information regarding the etiology of this condition, the following negative observations were made:

A. Penicillin and streptomycin administered in one case did not significantly alter its course.

B. Ergot and puerperal proteolytic enzymes were not involved.

C. The myocardial changes described are not specific.

D. There was no evidence of hypertensive disease, nephritis, hyperthyroidism, tuberculosis, rheumatic fever, rheumatic heart disease, dietary insufficiency, toxemia of pregnancy, or acute antecedent infection.

E. In only one of the cases was there a recognizable source of possible focal infection (lymphogranuloma venereum and past history of syphilis).

F. One patient received arsenical preparations, yet the myocardial lesions were diffuse rather than granulomatous as described in connection with hypersensitivity to this drug.

G. Blood cultures and animal inoculations with tissue extracts were negative.

H. The fetal structures were not affected.

4. Myocardial damage occurring at the peak of the physiologic circulatory burden of pregnancy was fatal in both instances.

5. Until something more is learned about the etiology of this condition it would appear that therapy should be directed toward support of the involved myocardium.

6. The hypotension may be correlated with the extent of myocardial involvement, and attempts to treat the former should not aggravate the latter.

The author wishes to thank Dr. R. Gordon Douglas for his critical review of the manuscript and valuable suggestions.

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FAILURE OF VITAMIN C, RUTIN, VITAMIN P, AND VITAMIN K IN THE TREATMENT OF PREGNANCY GINGIVITIS*

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THIS paper reports the failure of vitamin C,* rutin, vitamin P, and vitamin K in the treatment of the gingivitis and associated gingival hemorrhage frequently observed during pregnancy.

Incidence.—Since 1874, papers dealing with pregnancy gingivitis have appeared frequently in the literature.[1-13] Ziskin, Blackberg, and Stout[8] observed some form of pregnancy gingivitis in 70 per cent of pregnant women, comfirming the work of earlier investigators,[12] who found gingivitis in 53 to 60 per cent of pregnancies as opposed to 15 to 18 per cent in nonpregnant women. Maier and Orban,[12] however, although they observed that the gingivitis of pregnancy differs from simple gingivitis, could find no significant alteration in the prevalence of gingivitis in pregnant and nonpregnant women.

Pathology.—The clinical and microscopic picture of pregnancy gingivitis was completely described by Ziskin and Nesse.[10] They found that microscopically the most predominant changes in the gingivae and oral mucous membrane during pregnancy (loss of surface keratin, hydropic alteration of the stratum spinosum, hyperplasia of the stratum germinativum, and inflammatory changes in the lamina propria) were generally constant. The clinical picture, however, varied considerably even in different areas of the same mouth. Therefore, they classified the lesions clinically as follows: Class 1, bleeding from the gums (if present prior to pregnancy, then it was found in a more exaggerated form or upon less provocation); Class 2, appearance of glossiness, old-rose color, lack of stippling, edema, and blunting of the interdental papillae; Class 3, raspberry-red marginal gingivitis; Class 4, appearance of (a) hypertrophy of the papillae, (b) edema with hyperplasia of the epithelium of the interdental papillae, (c) papillae overgrowth simulating a pedunculated tumor, (d) proliferation of the undersurface of the free gum margin not including the papillae, and (e) pseudopapillae; and Class 5, pregnancy tumor. In all classifications, easily provoked gingival hemorrhage was an outstanding characteristic.

Etiology.—Pregnancy gingivitis has been variously described as resulting from autointoxication,[4] nonspecific inflammation,[5, 6] endocrine imbalance,[7, 10] and as an inflammatory condition probably of local irritative origin modified by the systemic changes incident to pregnancy.[11, 12]

Ziskin and Nesse[10] believed that the histologic picture arises as a manifestation of the changed nutritional, hormonal, and metabolic status during pregnancy.

Although vitamins are frequently prescribed to supplement the diet in pregnancy, a review of the literature revealed no investigation in which pregnancy gingivitis had been treated with vitamin C, rutin, or vitamin P. These therapeutic agents had as their rationale the increased capillary permeability

*Vitamin C, rutin, vitamin P, and vitamin K for this study were graciously supplied by the United States Vitamin Corp., New York, N. Y., through the courtesy of Dr. Louis Freedman.

and fragility, the suboptimal dietary vitamin C intake, and the suboptimal vitamin C content of the tissues and blood which have been reported as occurring during pregnancy.

Lowered levels of vitamin C in the blood during pregnancy have been reported by some investigators[14, 15*] but not by others.[16, 17] Gingival symptoms of vitamin C deficiency have been associated with low vitamin C blood levels during the course of pregnancy by some workers[14, 18] but not by others.[16] A relationship between a low vitamin C blood level and/or dietary intake and gingivitis has been described,[19, 20*] while it has also been denied that such a blood and/or dietary relationship exists.[21-23*] Some investigators have reported treating gingivitis successfully with vitamin C.[14, 19, 24*] Other workers have found vitamin C therapy without significant value under similar conditions.[25-27*] Some clinicians report efficacy of vitamin C medication in only a small percentage of cases.[28*]

Hesperidin methyl chalcone, the crystalline vitamin P[29*] preparation used in this study, is a flavone glucoside of hesperidin derived from the rinds of citrus fruits. It has been used with varying effect to control hemorrhage associated with increased capillary permeability.[30-34*] Vitamin C and vitamin P have been found to modify the deficiency states caused by the absence of each other and so are frequently administered together during vitamin P therapy.

Rutin, another flavone glucoside with one-half the vitamin P activity of hesperidin methyl chalcone,[35] has been used often with varying success (also frequently in combination with vitamin C) in treating diseases evidencing capillary fragility.[36-38*]

A relationship between vitamins P and C and vitamin K has also been suggested.[39*] Since there is evidence frequently of a vitamin K deficiency in late pregnancy[40] with associated hemorrhagic tendencies, vitamin K was included in this study.

Methods

Sixty-three subjects (aged 16 to 36 years) were studied. Fifty-one were in residence for the last 2 to 6 months of their pregnancies at a shelter for unwed pregnant women. Twelve were private patients. The 51 healthy, well-nourished shelter patients were a completely heterogeneous group. All showed definite evidence of gingivitis or gingival hemorrhage which, it was ascertained, was associated primarily with pregnancy. No cases of Ziskin and Nesse classifications 4c, 4d, 4e, or 5 presented for treatment.

Procedure.—The detailed chronological routine for each group, together with the drug dosage and schedule for vitamin C, rutin, vitamin P, and vitamin K and scalings,† appears as Table I.

Grouping.—Groups 1 and 2: Twenty-five unselected cases comprised the treatment groups, 1 (12 private cases) and 2 (13 shelter cases).

Group 3: Ten unselected patients, differing only from the routine of Groups 1 and 2 in that they received no medication, comprised control Group 3.

Group 4: Eight unselected patients constituted Group 4. They also received no medication but did receive conservative subgingival periodontal treatment at least once a week.

Group 5: Twenty unselected patients who received no treatment of any kind between the time of their initial examination and prepartal examination made up another control Group 5.

*Additional bibliographic references are available upon request to the author.

†The coronal scaling, as mentioned in the detailed procedure, is the important oral prophylactic measure which includes the scraping of the teeth at and above the gumline and the removal of debris and deposits therefrom, with maintenance thereby of consistent and adequate oral hygiene.

TABLE I. CHRONOLOGICAL DETAILED OUTLINE OF ROUTINE AND THERAPY WITH OBSERVATIONS ON THE EFFECT OF TREATMENT

DAY (APPROX.)	NO. PATIENTS: 1-12; 2-13 TREATMENT† GROUPS 1 & 2	AVERAGE* SEVERITY FOLLOWING THERAPY 1	2	NO. PATIENTS: 10 CONTROL† GROUP 3	AVERAGE SEVERITY FOLLOWING THERAPY	NO. PATIENTS: 8 SCALING‡ GROUP 4	AVERAGE SEVERITY FOLLOWING THERAPY	NO. PATIENTS: 20; CONTROL GROUP 5	AVERAGE SEVERITY FOLLOWING THERAPY
1	History and consult., full mouth periapical x-rays, exam., and original evaluation	4.2	4.1	History, full mouth periapical x-rays, exam., and original evaluation	3.9	History, full mouth periapical x-rays, exam., and original evaluation	3.8	Original evaluation	4.0
2-9	Prophylaxis and placebo, observation	4.4	4.2	Prophylaxis and placebo, observation	4.1	Prophylaxis and placebo, observation	4.0		
10-31	Vitamin C, 500 mg./day	4.1	4.0		4.3	3 conservative periodontal treatments‡	3.1		
32-53	Coronal scaling and vitamin C, 100 mg./day, and rutin, 40 mg./day	4.2	4.2	1 coronal scaling	4.5	3 conservative periodontal treatments	2.0		
54-75	Coronal scaling and vitamin C, 300 mg./day, and vitamin P, 300 mg./day	4.0	4.0	1 coronal scaling	4.4	3 conservative periodontal treatments	1.4		
76-81	1 coronal scaling, vitamin K, 4 mg./day	3.9	4.1	1 coronal scaling	4.2	1 conservative periodontal treatment	1.5		
82—to term delivery—14 post partum	Observation	4.1	4.4	Observation	4.6	Observation	2.0	Observation for varying periods of time	5.6

NOTE
TREATMENT

*0, absent.
2, slight.
4, moderate.
6, severe.
8, very severe.

†All patients were examined at least once weekly at which visits operative dentistry or oral surgery was frequently performed.

‡Conservative periodontal treatments included coronal scaling of the teeth and subgingival curettage.

Medication.—The following drug preparations were administered by mouth: vitamin C (as ascorbic acid, 100 or 250 mg. per tablet); rutin (20 mg. per tablet); vitamin P (as hesperidin methyl chalcone, 100 mg. per capsule with 100 mg. ascorbic acid); vitamin K (as menadione, 2 mg. per capsule); and placebo capsules (5 grains lactose per capsule).

Recording of Observations.—The rating of each patient at the outset was a composite of the observed severity of gingival changes and the hemorrhage incident to scaling. The ratings were recorded as follows: 0, absent; 2, slight; 4, moderate; 6, severe; 8, very severe. Immediately following the routine scaling (oral prophylaxis) at the conclusion of each treatment period, similar recordings were made to evaluate the medication and the progress of the patient during the just-completed therapeutic period.

Observations

Details of observations appear in Tables I and II.

Groups 1 and 2.—Vitamin C, rutin, vitamin P, and vitamin K were not found significantly effective in treating the gingivitis and/or gingival hemorrhage associated with pregnancy although no further increase in symptoms occurred during therapy. Any favorable changes were probably the result of the restorative dentistry and oral hygienic care (scalings, as in Group 3) received while under observation. No other favorable or unfavorable reactions to drug therapy were reported or observed.

Group 3.—Pregnancy gingivitis was arrested by monthly coronal scalings in these patients who, as in Groups 1 and 2, showed neither decrease nor increase of gingival signs or symptoms.

Group 4.—There was decided improvement of all cases in Group 4 who received weekly conservative periodontal treatments without drug therapy.

TABLE II. OBSERVATIONS UPON TREATMENT PLANS

GROUPS	TREATMENT	AVERAGE SEVERITY* OF PREGNANCY GINGIVITIS BEFORE TREATMENT	AVERAGE SEVERITY OF PREGNANCY GINGIVITIS FOLLOWING TREATMENT	ALTERATION IN SEVERITY
1, 2, 3, 4	Placebo and prophylaxis	4.0	4.2	+ .2
1 and 2	Vitamin C, 500 mg./day, for 3 weeks and monthly coronal scaling	4.3	4.1	− .2
1 and 2	Vitamin C, 100 mg./day, and 40 mg. Rutin/day for 3 weeks and monthly coronal scaling	4.1	4.2	+ .1
1 and 2	Vitamin C, 200 mg./day, and vitamin P, 200 mg./day, for 3 weeks and monthly coronal scaling	4.2	4.0	− .2
1 and 2	Vitamin K, 4 mg./day, for 1 week and monthly coronal scaling	4.0	4.0	0
1 and 2	Untreated observation period immediately prepartum	4.0	4.2	+ .2
3	Monthly coronal scalings alone	4.1	4.2	+ .1
3	Untreated observation period immediately prepartum	4.2	4.6	+ .4
4	Weekly or more frequent scalings	4.0	1.5	−2.5
4	Untreated observation period immediately prepartum	1.5	2.0	+ .5
5	No therapy	4.2	5.6	+1.4

*0, absent.
2, slight.
4, moderate.
6, severe.
8, very severe.

Group 5.—Gingival symptoms increased as pregnancy progressed when the patient remained without dental care.

Discussion

Gingival symptoms increased in Group 5 even with an optimum diet supervised by the staff physician and dietician of the shelter.

Subjective improvement was noted occasionally which was not evident clinically.

Increased symptoms were noted in Groups 1, 2, 3, and 4 after scalings were discontinued at the conclusion of each regime.

This study covered approximately one year, thereby minimizing the factor of seasonal variations in food and vitamin intake and resultant vitamin blood levels.

Since it is considered probable that vitamin C saturation must be accomplished before rutin or vitamin P can act effectively, it was deemed advisable to continue therapy on the same patients with the several drugs consecutively (thereby insuring any prerequisite saturation) if no significant clinical change was observed over any completed therapeutic period.

The symptoms of pregnancy gingivitis spontaneously regressed post partum although periodontal damage and caries remained in its wake when the gingivitis was left untreated periodontally.

This paper does not pass on the value of the above agents in the treatment of simple gingivitis or their efficacy in preventing the initial appearance or reappearance of pregnancy gingivitis.

Summary

1. Vitamin C, rutin, vitamin P, and vitamin K (frequently in combination) were not found significantly effective in treating the gingivitis or gingival hemorrhage associated with pregnancy.

2. Coronal scalings of the teeth were found to arrest the progress of these symptoms.

3. Weekly conservative subgingival periodontal treatments were observed to be the most effective means of controlling and alleviating the lesions under consideration.

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TRANSMUCOSAL ADMINISTRATION OF METHYL TESTOSTERONE, FREE TESTOSTERONE, AND TESTOSTERONE PROPIONATE*

A Clinical Comparison

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WHEN androgens first became available for therapy, ingested testosterone was found to be of little value. It was believed that the testosterone was for the greater part destroyed by gastric juices or inactivated by conjugation in the liver before reaching the systemic circulation. Later testosterone was rendered orally effective by methylation and found to have about one-third to one-fourth the potency of testosterone in similar dosage by parenteral administration.[1, 2, 3] Effectiveness of sublingual administration of steroid hormones was first observed by Freudenberger and Howard[4] in 1934, who reported premature opening of the vagina in ovariectomized immature rats after administration of small amounts (0.1 to 0.3 c.c.) of pregnancy urine into the oral cavity. Repeated observations of this effective mode of administration of steroids led to the current concept that absorption by mucous membranes of the oral cavity allows the steroids to pass directly into the systemic circulation thus eliminating destruction by gastric contents and inactivation in the liver.[5] Desoxycorticosterone acetate in propylene glycol-alcohol was the first steroid to be used clinically in this manner by Anderson[6] in 1940. Sublingual administration of progesterone was found effective by Greenblatt[7] and Corner[8] in 1944.

In 1942, Lisser, Escamilla, and Curtis[9] reported on the treatment of five cases of eunuchoidism and four of hypogonadism with testosterone propionate, free testosterone, and methyltestosterone in propylene glycol by this mode of therapy. In their series free testosterone was found more effective than methyltestosterone or testosterone propionate. The sublingual administration of testosterone has since been used by many investigators.[10, 11, 12] More recently, Lisser and associates[12] reversed their opinion when they reported a study of the relative effectiveness on libido of testosterone compounds given sublingually in various bases to twelve hypogonadal patients. Sublingual tablets of methyltestosterone, testosterone propionate, and "plain" testosterone were all found to be effective, and the degree of effectiveness was directly proportional to the daily dosage which was varied from 5 to 30 mg. With equal dosage, however, methyltestosterone was found to be more effective than "plain" testosterone, and the latter proved more effective than testosterone propionate.

*Acknowledgment is made to the following pharmaceutical houses which cooperated in this study: Chemical Specialties Inc., Syntex, S. A. (free testosterone and methyltestosterone linguets); Wyeth Incorporated (membrettes of free testosterone); Schering Corporation (buccal tablets of testosterone propionate, Oreton); and Ciba Pharmaceutical Products, Incorporated (methyltestosterone bucets, Metandren).

Method of Study

Sixty-three female patients with various gynecic disorders were given androgen therapy. In general, a course of therapy consisted of the administration of 15 mg. daily, for at least 30 days, of either methyltestosterone, free testosterone, or testosterone propionate prepared in hard compressed tablets for buccal absorption. Occasionally the dosage was varied from 4 to 30 mg. daily, depending upon the condition treated and the constitution of the patient. However, in only 107 courses of therapy, because of more or less similar dosage, could the data be utilized in this study in order to obtain a comparative index of the effectiveness of the various preparations. Patients were instructed to allow at least one-half hour for absorption of the tablets, during which time food and liquids were to be avoided. The suggested time of administration was after meals, or while resting, commuting, or reading.

Choice of Patients

Included in this series were only those patients who proved intelligent enough to cooperate thoroughly in this experiment, that is to say, those who were able to keep the tablet in the buccal pouch for a given length of time without continuously swallowing. Many of our clinic patients were excluded from this study because of poor intelligence and poor cooperation since they acknowledged permitting continuous swallowing of the dissolved medication. In these patients it appeared that methyltestosterone was far superior to free testosterone or testosterone propionate. Consequently, the series reported in this study is really a study on private patients who were reliable and capable of interpreting their subjective results.

Although the majority of the patients in this series had either dysmenorrhea or loss of libido as a primary complaint, other conditions for which transbuccal testosterone preparations were used included cyclic hypermenorrhea, premenstrual tension, endometriosis, dyspareunia, dysuria, cyclic headaches, and mastodynia. Evaluation was primarily on the basis of subjective response to therapy. When possible, individual patients were given the three preparations in varying sequence for thirty days, and in many instances placebo tablets were substituted in order to aid in evaluation of the comparative response to the different types of therapy.

Some factors considered in evaluation of comparative effectiveness of the various preparations were, when applicable, changes in libido, frequency of orgasm, relief of dysmenorrhea or dyspareunia, improvement in cyclic hypermenorrhea, relief of pain in mastodynia, and the incidence of acne, hoarseness, and, occasionally, mild hirsutism. Objective results of therapy such as regression of mazoplasia and incidence of mild hirsutism and hoarseness confirmed the present concept of transmucosal absorption and utilization of these androgenic steroids. For evaluation of comparative effectiveness, however, the subjective response of individual patients to the different preparations was of greatest importance. Each course of therapy was continued for at least thirty days in order to observe "lag time" in effect of therapy and "carry-over" effects of the therapy of the preceding month. Although the therapeutic effectiveness of all three preparations was readily observed, the comparative efficiency of these preparations in individual patients was difficult to evaluate. In many instances the response to a certain course of therapy varied considerably when repeated after several months of other types of therapy. Effects on libido, including frequency and ease of orgasm, were probably the most dramatic responses to therapy from the subjective standpoint. Interpretation of these abstract factors in evaluation is subject to daily fluctuation of environmental and emotional fac-

tors in the lives of patients as well as wide variation in integrity and attitude of individual patients toward open discussion of such intimate phases of their existence.

To elucidate some of these factors, a typical case history is presented in graphic form (Fig. 1). The study of this patient covers a three-year period of time, and although the results do not exactly reflect the average obtained in the entire series, this case is chosen because it proved to be our most reliable "weathercock" in evaluating the trend of effectiveness of the various androgenic compounds.

CASE REPORT.—This 36-year-old mother of four children consulted us because of extreme "nervousness" which was unaided by the therapy of a competent psychiatrist. The patient attributed the "nervousness" to her inability to attain sexual orgasm more often than once a year although she volunteered the information that she was "quite passionate." Other complaints included severe premenstrual tension associated with hypermenorrhea of eight days' duration in a regular 23-day cycle. Initial therapy consisted of methyltestosterone linguets, 15 mg. daily. By the fourth day the desired clinical response was attained, however, some edema of the extremities was apparent during this course of therapy. The dosage during the second month was reduced to 5 mg. daily and the side reaction was soon dissipated. But alas, with reduction in dosage the ability to have an orgasm was lost.

When given free testosterone, 30 mg. daily, the patient reported a marked increase in "well-being," nervousness was ameliorated, and there was no edema. She reported ability to achieve an orgasm "almost every time," and on one coition, twice. The menstrual period was reduced to a five-day normal flow rather than the usual eight days of heavy bleeding.

At the height of this blissful result the medication was changed for two months to progesterone, 10 mg. daily. The patient returned with indignant complaints that her medication must have been changed, that she was unable to attain a climax,[13] had seven- and eight-day heavy menstrual periods again, and was extremely nervous. It is interesting to note that free testosterone (30 mg. daily) given for two months following this course of progesterone therapy gave no improvement whatever in libido although it had given such excellent results previously. Methyltestosterone was again administered sublingually in 15 mg. doses daily and yielded very good results although some nervousness and tension persisted. At this point two pellets of testosterone (75 mg. each) were implanted subcutaneously and the patient reported a most ecstatic four months with orgasm "every time." The calculated rate of absorption of these pellets is equivalent to 1.5-1.0 mg. per pellet per day.[14] As the effect of the pellets began to wane, the patient was given free testosterone linguets, 20 mg. daily, with only minimal result as compared to the previous effect of the pellet implantation.

Methyltestosterone (15 mg. daily) which had given excellent results previously, offered no improvement over the free testosterone. Following this, however, free testosterone in dosage of 12 mg. daily then offered the same superlative results as the pellets, i.e., frequently two orgasms per coition.

During the next ten months free testosterone in half this dosage gave satisfactory results. During this period of time testosterone propionate was used for a month's time on two occasions, and the same excellent results were obtained—"never a failure." After all this, in the short time [illegible]ne month without therapy, the patient relapsed into a state of complete lack of sexual interest [illegible]r ability to have an orgasm.

We then endeavored to compare the effectiveness of methyltestosterone by ingestion with the previous observations. We also used diethylstilbestrol, a combination of diethylstilbestrol and methyltestosterone and a placebo in the same way. For the first month the patient received a tablet containing a combination of methyltestosterone (5 mg.) and diethylstilbestrol (0.25 mg.) three times daily by ingestion. The response was moderately satisfactory but in no way comparable to the preceding years of therapy with free testosterone, methyltestosterone, and testosterone propionate linguets. When this therapy was replaced by a

placebo tablet of identical appearance, however, the patient was again totally unable to attain an orgasm. After this, without knowing of a change in therapy, she reported gratifying results when given methyltestosterone in doses of 5 mg. three times daily. A subsequent course of diethylstilbestrol, 0.25 mg. three times daily, was accompanied by diminution in libido with only an occasional orgasm. This relatively poor response is in accord with previous observations that although estrogen therapy is occasionally accompanied by an increase in libido, many women devoid of sexual desire do not seem to respond in this manner to even massive doses.[13, 15]

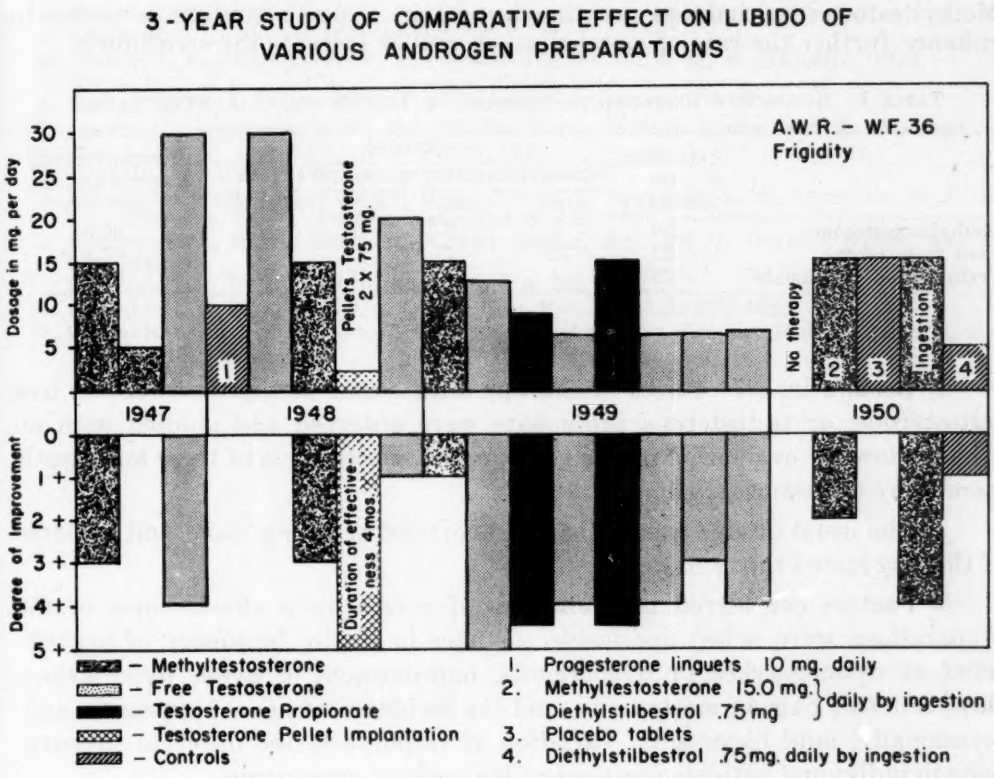

Fig. 1.

Discussion of Results

The response to transmucosal administration of methyltestosterone appeared significantly superior to both free testosterone and testosterone propionate in equivalent dosage. For purposes of this study estimation of effectiveness was based on physiologic effects attributable to androgen therapy, and results were classified as "satisfactory" for good or excellent results, and "unsatisfactory" for very slight or no results. Evaluation on this basis resulted in satisfactory results in 80 per cent of the courses of therapy with methyltestosterone, 67.3 per cent with free testosterone, and 64 per cent with testosterone propionate (Table I).

Although the methyltestosterone linguets appeared superior to free testosterone and testosterone propionate, there was no significant difference in the effectiveness of the latter two preparations. Since methyltestosterone is the only androgen which is effective when ingested, we may assume that the effectiveness of free testosterone and testosterone propionate depends on the

ability of the patient to allow for complete mucosal absorption since frequent swallowing of these preparations in salivary solution decreases their effectiveness.

The results of this study should not be construed to indicate that methyltestosterone is cited as the preparation of choice in all cases where oral androgen therapy is indicated. On the contrary, free testosterone or testosterone propionate may be preferable in certain conditions to methyltestosterone. Methyltestosterone is not always as well tolerated as some of the other androgens. Occasionally some patients experience nervousness and nausea. Methyltestosterone induces creatinuria and in hyperthyroidism it seems to enhance further the rate of metabolism as well as increase the creatinuria.

TABLE I. SUBJECTIVE RESPONSE TO THERAPY BY TRANSMUCOSAL ADMINISTRATION

	COURSES OF THERAPY	RESULTS				PERCENTAGE OF SATISFACTORY RESULTS
		UNSATISFACTORY		SATISFACTORY		
		NONE	SLIGHT	GOOD	EXCELLENT	
Methyltestosterone	30	4	2	19	5	80.0
Free testosterone	52	10	7	31	4	67.3
Testosterone propionate	25	4	5	13	3	64.0

Summary

1. Results in 107 courses of therapy with either methyltestosterone, free testosterone, or testosterone propionate were observed and studied with an attempt toward evaluation of the comparative effectiveness of these androgenic steroids by transmucosal administration.

2. The usual dosage was in the neighborhood of 15 mg. daily and a course of therapy lasted thirty days.

3. Factors considered in evaluation of comparative effectiveness of the preparations were, when applicable, changes in libido, frequency of orgasm, relief of dysmenorrhea or dyspareunia, improvement of cyclic hypermenorrhea, relief of pain in mastodynia, and the incidence of acne, hoarseness, and, occasionally, mild hirsutism. Variation of response to the different preparations in individual patients was used as the basis of comparison.

4. All three preparations of the androgenic steroids (methyltestosterone, free testosterone, and testosterone propionate) proved effective by absorption through the buccal mucous membrane in dosage of 5 to 30 mg. daily.

5. In general, some statistically significant difference in effectiveness of these preparations was shown when they were administered by mucosal absorption.

Conclusions

Satisfactory response to therapy was obtained in 80 per cent of the courses of therapy with methyltestosterone, 67.3 per cent with free testosterone, and in 64 per cent with testosterone propionate. Comparative effectiveness of these preparations in the individual patients gave a similar impression, i.e., that in equivalent dosage, testosterone propionate and free testosterone yielded more or less equally good results, but less dramatic results than those obtained with methyltestosterone. Since, unlike free testosterone or testos-

terone propionate, methyltestosterone is physiologically effective when ingested, we might attribute this greater effectiveness to utilization of the dissolved portion of the linguets which was inevitably swallowed during administration.

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MANAGEMENT OF THE TRANSVERSE LIE*

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THE management of transverse lie, even in the light of modern obstetrics, still presents many pitfalls. Keen judgment and technical skill are demanded from the time diagnosis is made until the patient is safely delivered. The relatively poor results in these cases have presented a challenge to the obstetrician for centuries. At first attention was focused on the technique of performing internal podalic version. Then the importance of correct timing was learned. Cesarean section became a useful alternative to version in the early part of this century, carrying with it new hazards. In recent times great strides have been made in antepartum measures, the conduct of labor, electing the most advantageous mode of delivery, and effectively applying supportive therapy.

In the second century A.D., Soranus of Ephesus[1] first described a technique for internal podalic version in transverse lie. The technique has undergone an evolution of gradual improvement. For centuries version was done through a partially dilated cervix and breech extraction performed after the cervix became completely dilated. This was accompanied by a very high fetal mortality. It was not until 1886 that Winter[2] stated that version should be done after the cervix attained full dilatation, and breech extraction should follow immediately. This was not easily accepted, and the controversy that followed was not resolved for thirty years. Among the corroborative studies, that of Sachs and Poeck,[3] in 1926, was the most outstanding in emphasizing the importance of early rupture of membranes. The following year Kamniker[4] reported a similar study and included cases of delivery by transperitoneal and extraperitoneal cesarean section; these were rare instances. Puppel in 1931[5] stressed the role of contracted pelvis as a cause of transverse lie. The next year Chatunzew[6] advised that if membranes rupture when the patient is not deliverable, cesarean section is mandatory. In America the better understanding of transverse presentations essentially began in 1932 with the excellent study by Eastman.[7]

Since 1932 there have been six comprehensive reviews of this subject. The present series encompasses the experience at University Hospitals (MacDonald House) for the past twenty years. To conform with the definitions of other writers, transverse lie is defined as occurring when the long axis of the fetus crosses the long axis of the mother obliquely or at right angles. Excluded are cases occurring in twins, and those of spontaneous evolution, spontaneous version, and "partus conduplicato corpore." The birth weight is used as the criterion of maturity. Infants of 2,500 grams or over are considered as full term, and from 1,500 to 2,499 grams as premature.

Incidence.—In the 54,000 deliveries from 1929 through 1948 there were 73 cases of transverse lie, an incidence of 0.14 per cent, closely approaching the figures of Cole,[8] 0.17 per cent, and of Johnson,[9] 0.20 per cent. Actually, if all cases of transverse lie which undergo spontaneous version were known and included, the incidence, particularly in the premature group, would be consider-

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ably greater. Fifty-three of the infants in our 73 cases weighed over 2,500 grams. There were 19 cases occurring in Negroes, 26 per cent of the total, while the clinic proportion of Negroes was almost 22 per cent.

Etiology.—An etiological agent of transverse lie is one which tends to deter the fetus from occupying its usual longitudinal polarity. In Table I it is seen that multiparity (two or more previous viable pregnancies) was the presumed etiological agent in 18 cases, 24.7 per cent. However, of the entire group only 23.3 per cent had had three or more previous children. This is in marked contrast to an occurrence of 46 per cent in Johnson's cases and 54.9 per cent in those of Harris.[10]

TABLE I. PARITY

PARITY	CASES	PER CENT
0	16	21.9
1	24	32.9
2	16	21.9
3	3	4.1
4	5	6.9
5	3	4.1
6 or more	6	8.2
	73	100.0

Most impressive was the finding of placenta previa in 16.4 per cent of our cases. Harris found a correlation of 15.3 per cent, Cole 10 per cent, and Eastman 5.4 per cent. Stevenson,[11] using placentography and cystograms on transverse presentations within the last ten weeks of gestation, found an incidence of 26.8 per cent; it is not known how many of these underwent spontaneous version before delivery.

In three cases, 4 per cent, a mass was obstructing the pelvic inlet. These were a uterine myoma, a cervical myoma, and a large fibroid tumor of the ovary. Contracted pelvis was found in 9 instances, 12.3 per cent; prematurity was the cause in seven cases; two cases were due to uterine malformations; and one each to polyhydramnios, insertion of Voorhees bag, and excessive-sized infant (over 4,000 grams). Many cases had several contributing factors. In each instance the most likely cause was designated. For a large group, 26 per cent, the etiology was unknown. Perhaps, if these had had soft tissue x-ray studies, some might have been explained by fundal implantation of the placenta. As Stevenson pointed out, a placenta in the fundus would occupy a large part of the available space at the upper uterine pole, thus displacing the infant. We have excluded as possible etiologies premature rupture of membranes, relaxed abdominal wall, and dead fetus. These are not believed to be primary causes.

TABLE II. ETIOLOGY

CAUSE	CASES	PER CENT
Multiparity	18	24.7
Placenta previa	12	16.4
Contracted pelvis	9	12.3
Prematurity	7	9.6
Polyhydramnios	1	1.37
Voorhees bag	1	1.37
Bicornuate uterus	1	1.37
Arcuate uterus	1	1.37
Cervical fibroid	1	1.37
Uterine fibroid	1	1.37
Ovarian fibroid	1	1.37
Excessive-sized infant	1	1.37
Unknown	19	26.0
	73	100.0

Labor.—The average duration of labor for those patients delivering full-term infants by version was 15.5 hours for primiparas, and 9.9 hours for multiparas. Labor was somewhat shorter for those delivering premature infants. One patient was allowed to labor 69 hours before delivery of a healthy infant. She had a postpartum hemorrhage due to uterine atony and hysterectomy was done to control bleeding.

There were nineteen cesarean sections done before the onset of labor. In all but two of these the indications were indisputable. Of those who had some labor prior to section, primiparas averaged 13.2 hours and multiparas 12.7 hours.

Delivery of Full-Term Infants.—There were 53 infants in this group; 24 patients, 45.3 per cent, were delivered by internal podalic version, and 29 patients, 54.7 per cent, were delivered by cesarean section. Seven of the infants were delivered dead or died in the neonatal period, five after version and two after section. Of the 19 version babies delivered alive 5 had ruptured membranes before the onset of labor, and 6 ruptured membranes during the first stage. In those 11 instances version was done under deep ether anesthesia, and with the utmost caution. In the remaining cases, membranes ruptured at or shortly before delivery. Two instances of prolapsed cord occurred. In one case the cervix was fully dilated and the patient was delivered successfully. In the other, representing one of the five deaths in this group, the prolapse occurred with the cervix two fingers dilated. The cord was replaced, and a Voorhees bag was inserted intraovularly. The infant died of asphyxia. Two others of the 5 also ruptured membranes early, one neglected home delivery with a long labor, the other delivered with two tight loops of cord about the neck. The remaining 2 cases of the 5 version deaths ruptured membranes shortly before delivery. One infant was lost because of difficulty with the breech extraction. The other died during early labor due to the mother's severe pre-eclampsia (autopsy on infant).

Twenty-nine full-term infants were delivered by cesarean section. Two died. One died prior to admission, the section being done for placenta previa. In the other case membranes ruptured prematurely; the patient was allowed to stay in labor thirteen hours, and section was finally done when fetal distress occurred.

Fetal Mortality.—Eastman, in a study of 93 cases between 1896 and 1931, reported a fetal mortality of 30 per cent. Harris and Epperson, in a comparative study from the same hospital covering the years from 1931 through 1948, reviewed 91 cases with a fetal mortality of 14.3 per cent. Johnson's 99 cases covering 45 years had a fetal mortality of 36.5 per cent. Mortality figures excluded those cases where no fetal heartbeat was heard on admission. Cole and Delaney noted, in their 63 cases of full-term infants, a mortality of 14.5 per cent, corrected to 8.6 per cent. Using similar criteria, the fetal mortality at MacDonald House in the twenty years ending 1948 was 13.2 per cent, correctable to 9.4 per cent. In retrospect the errors in the management of our cases seem readily apparent. Encouragement is derived from the downward trend of fetal loss in transverse lie in our own as well as other hospitals.

Delivery of Prematures.—Of the 20 cases in this group, 6 were delivered by section, and 14 by version. Three prematures lived after version. In all 3 cases membranes ruptured shortly before or at delivery. To consider the 11 deaths in the version group, 4 died prior to the onset of labor; 2 were monsters; 1 died due to premature separation of the placenta; and 4 died during labor. Of the 4 who died during labor their were 3 cases in which membranes ruptured before the onset of labor or early in the first stage. The fourth died of asphyxia with a loop of cord tightly about the neck. The only 2 infants who died after cesarean section both had congenital pulmonary atelectasis on postmortem

examination. These two sections were done for severe rheumatic heart disease and for premature rupture of membranes in a patient who had had a previous section.

Because there are so many factors determining survival of the premature infant, to conjecture how many of those lost might have been salvaged would be somewhat presumptuous. The results do indicate that the premature infant seems to tolerate labor very poorly after membranes have ruptured.

TABLE III. DELIVERY RESULTS

	FULL TERM				PREMATURES			
	CASES	PER CENT	DIED	PER CENT	CASES	PER CENT	DIED	PER CENT
Section	29	54.7	2	6.9	6	30	2	33
Version	24	45.3	5	20.8	14	70	11	78.6
Total	53	100.	7	13.2 (corr. 9.4%)	20	100	13	65 (corr. 25%)

Maternal Morbidity and Mortality.—Nine of 38 mothers, 23.7 per cent, who delivered vaginally, had a febrile postpartum course. In sharp contrast, 17 of 35 mothers, 48.6 per cent, delivered by section, had a morbid course. A large majority of cases in both groups occurred before the era of chemotherapy and antibiotics. There was one maternal death, an incidence of 1.4 per cent.

M. L., Hospital No. 26142, a 42-year-old white primigravida with the estimated date of confinement Sept. 1, 1930, was admitted in false labor on July 14. The fetus was presenting by right sacrum anterior; membranes were intact. After twelve hours labor began spontaneously with 3- to 4-minute contractions of moderate intensity, and a small amount of bloody show. The fetal heart was regular at 142 beats per minute. The cervix dilated to 2½ fingers in the next 3 hours, and morphine-scopolamine medication was begun. In the next 25 hours of labor she made virtually no progress. She took 200 c.c. of water by mouth, voided 550 c.c., and vomited 100 c.c. A low classical cesarean section was done under nitrous oxide-oxygen anesthesia because of a history of pulmonary tuberculosis (current chest x-ray was negative). An apparently normal 2,790-gram female was delivered in good condition. Placenta and membranes were removed intact. During the first two postoperative days her temperature ranged between 38.3° C. and 40.6° C. She was distended, but took some fluids and was voiding. On the third and fourth postoperative days the temperature approached normal, but she began vomiting. The red count was 4.4 million, white count 10.3 thousand. The urine showed 3+ albumin, and had a specific gravity of 1.023. The lochia now became foul. The abdominal distention increased, and the vomiting increased. Intravenous fluids were started. On the fifth day the temperature rose steeply. Efforts to decompress the abdomen had been useless. Vomiting continued, but no fecal odor was noted. Enemas were expelled, but nothing else was passed by bowel. The abdomen became generally tender. With a diagnosis of paralytic ileus and generalized peritonitis, surgical consultation was obtained. An ileostomy was done under local anesthesia on the evening of the fifth day. Her condition rapidly became worse. She became comatose. The temperature continued to rise. She died on the sixth postoperative day. Postmortem examination revealed acute gangrenous endometritis and myometritis, acute fibropurulent peritonitis, cloudy swelling of the viscera, and normal lungs.

Comment

With our own experience combined with that of others, the management of transverse lie falls into a sequence of logical steps. After the diagnosis is made, either by palpation or x-ray, investigation for the cause should be made. In a primipara the presence of transverse lie must always be considered to indicate

coincident pathology until it is proved otherwise.[12] An accurate knowledge of pelvic measurements is imperative. Placenta previa and fundal implantation of the placenta can be demonstrated by soft tissue x-ray and cystograms. The x-ray can help detect pelvic obstructing tumors, fetal monsters, and excessive-sized infants. Without contraindication to vaginal delivery, external cephalic version should be attempted and repeated, if necessary, beginning in the third trimester. Most of these can be done as an office procedure; about 20 per cent[13] will require anesthesia to obtain adequate relaxation. About one-fourth[14] of cases can be expected to undergo spontaneous version either in the last part of pregnancy or early in labor.

While in labor the patient should be observed carefully for rupture of membranes and prolapse of the umbilical cord. Though we were unusually fortunate in encountering only two cases of prolapsed cord, this is a common occurrence, and carries with it a high fetal mortality.[15] The intraovular use of the Voorhees bag in transverse lie has been almost universally discarded. Our own limited experience with it has been unhappy. The vaginal use of the bag was recommended by DeLee[16] and in breeches by Vignes.[17] By offering counterpressure its aids in preventing rupture of membranes. We used it this way once, successfully.

The patient should not be abandoned in labor to the point where she represents a poor operative risk. Prolonged labor leading to uterine contraction ring ("hour-glass contracture of the uterus"—Eastman) and uterine atony are to be avoided. When membranes rupture internal podalic version and breech extraction should be done if the cervix is completely dilated, no contraction ring is present, too much amniotic fluid has not escaped, no disproportion exists, and there is no contraindication to ether. Though eleven full-term infants were successfully delivered by version after early rupture of membranes, there were three who died. This is a relatively high fetal mortality. Labor after rupture of membranes was very poorly tolerated in the premature group. None were delivered by version after early rupture of membranes. Deep ether anesthesia, either by open-drop or closed system, was used on all patients delivered by version. This is especially important if there is a limited amount of amniotic fluid present at the time of version. We had no case of ruptured uterus, but it has occurred frequently in other series.[18, 19] Why these occurred it is difficult to say, but we believe that if attention is paid to technique, anesthesia, and the available amount of amniotic fluid, version is a relatively safe procedure.

The recent trend toward the more liberal use of cesarean section has greatly reduced fetal mortality. But section is not a panacea. In this series there was twice as much maternal morbidity that followed section as followed version. Our only maternal death followed cesarean section. The free use of antibacterial drugs[20] and the judicious use of extraperitoneal cesarean section in the infected or potentially infected case will reduce the incidence of postpartum infection appreciably. Antepartum evaluation will filter out those patients who should not be allowed to go into labor. The most difficult problem is presented by those cases in which the membranes rupture during labor. If delivery is anticipated within a short period of time, and too much amniotic fluid has not been lost, labor should be allowed to continue. But if these conditions do not pertain, or if the infant is premature, one would be inclined to do a cesarean section.

Summary and Conclusions

1. Clinical appraisal and x-ray studies should determine those cases which should not be allowed to go into labor.

2. Where there is no contraindication, external version should be attempted.

3. If membranes rupture during labor, section should be considered unless vaginal delivery is anticipated within a short period of time.

4. Used with good judgment, internal podalic version is a safe mode of delivery. Cesarean section is an alternative procedure, and should be done when there is definite indication.

5. Supportive therapy, such as intravenous fluids, blood transfusion, and antibacterial agents, should be used liberally.

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USE OF AN ANTIDEPRESSANT ANALGESIC IN THE POSTPARTUM AND POSTOPERATIVE STATES

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THE postpartum and postoperative period is often a trying experience. In addition to more or less physical discomfort there is usually an emotional letdown—the so-called "calm after the storm"—which may make the patient indifferent or even resistant to measures designed to hasten recovery. In the postpartum patient, this convalescent depression is so common that nurses refer to it casually as "baby blues." This is especially true of the primipara, who often faces the future with mixed emotions of joy and fear when she contemplates the many-faceted responsibilities of caring for her new baby. Treatment of the physical component of this postoperative malaise is a routine matter. The emotional distress, on the other hand, is not only usually ignored, but often is actually aggravated by the medications used in treating pain.

The drugs most frequently prescribed during this period—salicylates, codeine, and barbiturates—are depressants as well as analgesics. Furthermore, about 90 per cent of hospital patients are given a bedtime hypnotic, consequently a morning lethargy is not uncommon. It is a matter of common observation as well as a scientifically established fact that[1] the pain threshold is influenced by mood; the depressed patient dwells on his troubles, including pain, and "attention acts like a magnifying glass"; the complaint of pain usually leads to more medication; so a vicious cycle of pain-analgesia depression is established.[2]

Logically, an analgesic should effect mental, as well as physical, well-being. It is well known that the amphetamines have a marked antidepressant effect.[3] One of these drugs, Benzedrine* (d,l,amphetamine), is combined with aspirin and phenacetin in the analgesic known as Edrisal*; we have found it suitable and helpful in treating moderate postpartum and postoperative pain.

Procedure

Our first trial of Edrisal was in a multipara who was experiencing severe "afterpains." In spite of repeated doses of aspirin, codeine, and phenobarbital, she obtained little relief and became more depressed and more uncomfortable. Because of reported good results from its use in dysmenorrhea[4, 5] Edrisal was prescribed. Within an hour after taking two tablets, the patient's mood brightened, she got out of bed, and reported to the nurse that she had not "felt this good for quite a while."

*Trade-mark names of Smith, Kline & French Laboratories, Philadelphia.

Because of this excellent response, it was decided to prescribe Edrisal routinely in the postpartum and postoperative period, in an attempt to assess its value as an analgesic. In the past two years Edrisal has been administered to 350 patients, of whom 320 were postpartum and 30 postoperative. These cases were unselected and consecutive, and included various obstetrical and gynecological procedures. With but few exceptions they were carefully supervised private patients of the author. All were hospitalized, and thus under close scrutiny. Neither the patients nor the nurses knew the nature of the medication prescribed. Since many of these patients also received other medicaments of similar appearance, such as stilbestrol or methyl tetosterone to suppress lactation, they were not even aware of our purpose in prescribing "No. 3494" (our code number for Edrisal).

Administration and Dosage

Postpartum patients were started on Edrisal the day following delivery. Postoperative patients with more severe pain were given Edrisal as soon as administration of morphine or "Demerol" was discontinued, i.e., usually on the second or third day.

Each tablet of Edrisal contains acetylsalicylic acid 2.5 grains, phenacetin 2.5 grains, and Benzedrine Sulfate 2.5 mg. After a number of trials, the optimum daily dosage of this combination was established as two tablets at 9 A.M., and 1 or 2 tablets at 2 P.M. This schedule was used in about 90 per cent of the series, the time interval being chosen to maintain a "bright" attitude during the day, without producing insomnia. (The Benzedrine in Edrisal has a "waking" as well as an antidepressant effect.[3]) In the remaining 10 per cent of the series, in whom discomfort and pain were more intense, two Edrisal tablets were prescribed every four hours, but not after 6 P.M. Most of the patients took Edrisal for an average of seven days.

Results

The therapeutic effect of Edrisal, especially when discomfort is associated with depression, is usually remarkable. In this series, 344 of the 350 patients showed a good response. Pain was adequately controlled. The analgesia produced by two tablets of Edrisal compares favorably with that obtained with a combination of ½ grain codeine and 10 grains aspirin, and the emotional response is far better. The advantages of the mental and physical stimulation produced by Edrisal cannot be emphasized too strongly. Patients who had been unwilling to try early ambulation because of lassitude, fear, or indifference, often showed a rapid change of attitude. They became more confident and cooperative after taking Edrisal, and often got out of bed voluntarily. Though the nursese did not know the purpose of the drug, they noted spontaneously that these patients were more alert and active.

One patient delivered of her third baby deserves special mention. Following both previous deliveries she had experienced a mild but definitely psychotic postpartum depression. On the fourth day after delivery of the third child, the nurses and resident noticed that this patient again was moody, depressed, and showed little interest in her surroundings. She was given two Edrisal tablets every four hours during the day. Her mood brightened, she became interested in her baby, and was in suitable condition for discharge at the usual time, i.e., on the eighth postpartum day. When seen after a six weeks' interval her outlook, unlike that in the two previous instances, appeared to be normal. While it is impossible to judge whether or not the depression which was manifest on the fourth day might again have developed into a psychosis, there is little doubt that the mood was abruptly changed by admin-

istration of Edrisal. With such patients it is possible that the breaking of a depressive cycle or giving of a temporary lift during the most difficult days may avert serious developments.

Only six of the 350 patients reacted unfavorably to the drug. Three of these complained of severe "heartburn" which disappeared when the drug was withdrawn. In two cases a mild hyperthyroidism had apparently been overlooked and these patients showed evidence of overstimulation—marked physical and mental irritability, "jitteriness," tremor, and insomnia. These symptoms disappeared when the drug was discontinued. The sixth patient, oddly enough, complained that the pills made her sleepy, telling the nurse that she "did not want any dope"; a correct evaluation of this response is difficult. The remaining 344 patients showed no untoward response to Edrisal.

In some instances more or less "letdown" was experienced when the medication was stopped; such patients called after being home a few days to request a further supply of tablets. This letdown rapidly disappears, however, without treatment. No case of habituation or refusal to stop the medication was encountered.

Comment

Although Edrisal has been available for some time, its use in the postpartum and postoperative state has not, to our knowledge, been reported.* Our observation of the 350 patients in this series has enabled us to formulate some conclusions concerning the indications and contraindications for its postpartum and postoperative use. In our opinion, Edrisal is indicated wherever there is mild to moderate discomfort, especially when there is an associated depression. While it cannot be expected to give the degree of analgesia produced by morphine or Demerol, Edrisal proved to be an entirely adequate substitute for ordinary doses of codeine in this series of patients. This rather surprising potency is probably due to the Benzedrine component, which has three important effects: first, Benzedrine is known to have considerable analgesic activity in its own right.[7] Second, it probably potentiates the action of the aspirin and phenacetin in the combination. It is well known[2] that the combining of analgesics seems to give more than merely additive effect; and d-amphetamine has been reported to potentiate the analgesic effect of morphine.[8] Third, and perhaps most important, is the marked antidepressant action which has already been discussed.

Edrisal seems indicated also whenever there is lethargy which may interfere with early ambulation, whether the lassitude is produced by drugs or not. It might be noted here that in postoperative and postpartum patients without pain but with depression, we have often used Benzedrine or Dexedrine alone with excellent results, but these cases are omitted from the series. The only contraindication to use of Edrisal is hypersensitivity to Benzedrine, aspirin, or phenacetin. In our experience, this is uncommon. Hyperthyroid patients may be overstimulated by Benzedrine, and aspirin very occasionally causes gastric distress, but we found only 2.1 per cent of our 350 patients unable to tolerate Edrisal.

Summary and Conclusions

1. Depression, a common aftermath of postpartum and postoperative procedures, is deepened by the analgesics and sedatives ordinarily used to relieve pain. Since depression increases awareness of pain, continued treatment leads to the establishment of a vicious cycle.

*Just recently, Barnett[6] reported using Benzedrine and Dexedrine (d-amphetamine sulfate, S.K.F.) to hasten ambulation following ear, nose and throat surgery.

2. To be most effective, an analgesic should relieve depression as well as pain. Edrisal, a combination of aspirin, phenacetin, and the antidepressant Benzedrine, fulfills these requirements.

3. In 350 postpartum and postoperative patients treated with Edrisal, results were uniformly good. The analgesic effect of two tablets of this combination compares favorably with that of ½ grain codeine plus 10 grains aspirin. In addition, it brightens the patient's moods, making them more alert, active and co-operative.

4. None of the patients showed serious side reactions to Edrisal. In six the drug was discontinued because of "heartburn" (3 cases), overstimulation (2 hyperthyroid cases) or "sleepiness" (1 case). The remaining 344 had no ill effects.

5. Since the mental and physical stimulation provided by Edrisal encourages early ambulation, it is considered more appropriate for postpartum and postoperative use than the depressant analgesics.

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TREATMENT OF ACUTE PUERPERAL MASTITIS*

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THE advent of early and adequate penicillin therapy in the treatment of acute puerperal mastitis has lowered the incidence of suppurative lesions. However, the disease continues to remain a serious complication on an obstetric service. Thus the continued effort is made (1) to prevent puerperal mastitis and (2) to avoid suppurations. The destruction of tissue as a result of suppuration not only may endanger life, but may be associated with recurrent abscesses and interference with lactation by necessity of discontinuance of nursing. Formerly, the treatment of acute mastitis was drying up of the breasts and then incision of any abscesses that might develop. Later, sulfonamides were found to lessen the incidence of suppuration if adequate doses were given within the first twenty-four hours; but when suppuration became inevitable after sulfonamide therapy failure, the formation of the abscess proceeded very slowly, often requiring several days for proper tissue changes.

Hodgkinson and Nelson[1] reported no cases of suppuration in twenty-four cases of acute mastitis treated with penicillin. Penicillin was given by Power and Cravotta[2] with cures obtained within forty-eight hours in twenty-five cases. Hesseltine, Freundlich, and Hite[3] reported twenty-three cases of acute mastitis treated with multiple small doses of penicillin (30,000 every three hours) with six cases requiring incision and drainage of abscesses. The incidence of acute puerperal mastitis with abscess formation was 0.51 per cent over a 13½-year span. These latter authors by the cultural studies of the breast abscesses found practically always *Staphylococcus aureus* (hemolytic and coagulose positive) as being the offending organism. The penicillin resistance of the staphylococcal strains cultured varied from 0.006 to 6.25 units per cubic centimeter of penicillin. The resistance of strains requiring a high concentration of penicillin exceeds the anticipated blood level of penicillin in treatment of patients with the then current dosage of this antibiotic. It is plausible that some of the strains studied acquired their resistance during antibiotic therapy. Hesseltine, Freundlich, and Hite recovered *Staphylococcus aureus* from the nasopharynges of twenty-one out of thirty babies within the first ten days of life. Obviously, then, the nursing baby is a primary source of contamination of an injured, fissured, or traumatized nipple in two out of every three patients.

The greater portion of our cases of mastitis occur within the first six weeks of the puerperium. Observations beyond this time have been limited due to the small number of mothers nursing beyond this period. In 1947-1948 there

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were forty-eight cases of mastitis, an incidence of 1.2 per cent, with nine cases requiring incision and drainage or an uncorrected incidence of 22 per cent suppurative cases. However, in five of these, the abscess was present on admission. Four of the remaining forty-three patients went on to suppuration while on penicillin therapy. This represents an actual failure incidence of 9.3 per cent. The routine therapy at that time was 30,000 units of crystalline penicillin every three hours (240,000 units per 24 hours). In the same series there were five patients who had a second hospitalization for treatment of the inflammatory process. Suppuration was prevented in all these five. The immediate results not only revealed nine mothers with mammary abscess, but nine other patients had residual induration of the breast at the time of discharge from the hospital. However, it is noteworthy that not one patient had a residual induration when seen six weeks post partum.

The lowered incidence of abscess formation from the previous year, by increased dosage of penicillin, led to a further change in the routine therapy. In 1948-1949 the dosage was increased to 300,000 units of penicillin in oil twice daily (a total of 600,000 units per 24 hours). Within one year, 4,081 mothers were delivered, and in this number occurred forty-two cases of acute mastitis, or an incidence of 1.03 per cent, which comes within the range observed in previous years at this maternity hospital. Of the forty-two cases, three patients were admitted to the hospital with abscesses present and without adequate therapy previously, while only two with acute mastitis who were placed on the newer therapeutic program went on to abscess formation. This is two out of thirty-nine patients, or 5.1 per cent failure rate, less than one-half of the former rate.

The forty-two patients were seventeen primiparas and twenty-five multiparas whose ages ranged from 18 to 44 years. The right breast was affected in sixteen cases; left, twenty-four; and the mastitis was bilateral in two. Not one of these patients developed recurrence of the inflammatory process in either the same breast or the opposite; thus the increased amount of penicillin not only reduced the number of abscesses, but also of recurrences.

To emphasize further the need for even greater amounts of penicillin and earlier institution of therapy for still better results, reference is made to the year 1949-1950. Every patient with acute mastitis was immediately hospitalized. All nursing or breast pumping was immediately discontinued. The breasts were well supported and kept at rest. Ice bags were used only as the patient desired, and codeine and aspirin were used for control of pain. Penicillin was given in amounts of 600,000 to 800,000 units at once, and then 300,000 to 400,000 units (depending upon the product in stock) were administered three times daily at eight-four intervals (900,000 to 1,200,000 units daily) until of forty-eight hours with normal temperature elapsed, after which the penicillin dosage would be reduced gradually. This series consisted of 35 patients with acute mastitis; an incidence of 0.59 per cent with not one case of abscess formation. Thus we have a total of nonsuppurative mastitis on admission in the last two groups of 74 treated by increasing dosage of penicillin. Of these 74, only two patients developed a mammary abscess, a failure rate of 2.7 per cent (Table I).

The complete prevention of this complication, which may occur not only in the early puerperium but later, has yet to be found. Hesseltine and associates studied the use of penicillin ointment prophylactically in nursing mothers. Their study did not support the view that the use of penicillin ointment would reduce the incidence of mastitis. Substances used to soften or harden the areola are not recommended at this clinic, inasmuch as the areola and the nipple are managed as normal skin.

Routine cleansing of the areola with sterile water prior to and after nursing remains one of the basic methods in the care of the lactating breast. Separation of patients with contagious disease, and skin lesions, as well as exclusion of medical, nursing, and all other personnel with the same type of lesions from the mother and baby is imperative.

Prophylactic measures can be advantageous in the prevention of breast abscess, but such steps need not be abuses. For instance, if every mother did not nurse her baby the risk would be reduced to the minimum, but this seems too great a price to pay from the viewpoint of the baby as well as the mother. Nursing mothers should be properly instructed in the hygienic care of the breasts and nipples: keep the nipple as exposed to the air as is feasible and avoid prolonged nursing. Whenever fissured or cracked nipple develops, or any symptom is noted in the breast, the patient should notify the nurse if she is in the hospital, or call her physician if she is at home. Rest for an infected breast is as sound as rest for any other infected organ.

TABLE I. INCIDENCE OF PUERPERAL NONSUPPURATIVE AND SUPPURATIVE MASTITIS IN COMPARISON TO THE NUMBER OF WOMEN DELIVERED OVER A 17-YEAR PERIOD

YEAR	MOTHERS	MASTITIS (NO.)	PATIENTS HAVING ABSCESSES		MINIMUM DAILY DOSE OF PENICILLIN
			NO.	PER CENT	
1933-47*	40,629		210	0.51	
1947-48	4,068	48	9	0.22	240,000
1948-49	4,081	42	5	0.12	600,000
1949-50	3,931	35	0	0.00	900,000 to 1,200,000
Totals	52,709		224		

*1933-47 from Hesseltine, Freundlich, and Hite.[3]

Comment

From these facts has come the establishment of better observation of the patient in the hospital, and more thorough instruction to the patient when she goes home to report promptly and immediately any symptoms or complaints about the breasts. It is obvious that the elimination of contributing factors, as fissured or cracked nipples, will reduce the incidence of mastitis. Even without predisposing conditions, the rate of mammary suppuration increases as time lapses from the onset of the inflammatory process to the time of institution of therapy. The institution of therapy means complete rest of the infected structure and adequate antibiotic therapy promptly and regularly. The breast is rested by: (1) supporting brassiere or binder, (2) ice bags as elected by patient, and (3) immediate and complete discontinuance of nursing, breast pumping, or manual expression. The patient should be particularly instructed not to use heat locally nor to massage the breast.

Although some of the other antibiotics do have therapeutic effect in staphylococcal infection, penicillin has been employed more extensively and very successfully. The reason for 600,000 to 800,000 units initially is that some strains of *Staphylococcus aureus* hemolytic will have resistance up to 6.25 units per cubic centimeter. The daily dosage of penicillin should approximate 1,000,000 or more units given in pharmacologic program for an adequate and sustained level. The combined crystalline and slow-absorbing penicillin may be

used throughout the period of therapy. The initial therapy should contain an ample amount of the rapid-absorbing penicillin.

Persistent residual masses in the breasts may be sharply walled off abscesses. The patient may become afebrile and have a normal white count in these instances. Consequently, if an induration or localized lesion does not vanish in a reasonable time, aspiration by a large needle should be done to exclude a "localized abscess."

The time interval from the first symptom to the institution of therapy is related directly to the success of the therapy. Surgical incision of breast abscess is not more difficult than simple drainage of any other abscess but the anatomy of the breast must be recognized. The septa of the breast not only force the surgeon to wait until the abscess is well formed, but necessitate adequate deep incision radiating from the areola with the nipple as the center point. The cavity is loosely packed to control bleeding for 18 to 24 hours and then the pack is removed gradually over the next day or few days, depending upon the size of the cavity. Gentleness is important. Since the wound must heal from the bottom of the abscess cavity, the skin must be kept apart.

Conclusions

1. A report is made of observations on 74 cases of acute puerperal mastitis. Suppuration occurred in only two patients who were admitted to the hospital before an abscess was evident. The therapeutic regime of 600,000 to 800,000 units of penicillin daily in divided dosage has been effective in prevention of suppuration. It appears that the amounts of 900,000 to 1,200,000 units cause even more rapid response, and thus are positively indicated.

2. The time interval from the first symptom to the institution of therapy is related directly to the success or prevention of abscess.

3. The dosage of antibiotic may seem out of proportion to that needed to maintain adequate blood level; nevertheless, the results have warranted the therapeutic regime outlined.

The authors thank Merck & Co., Inc., for the generous supplies of penicillin used for the major portion of this study.

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Department of Case Reports
New Instruments, Etc.

RUPTURE OF A VULVAR VARIX WITH MASSIVE AND EXTENSIVE HEMORRHAGE FOLLOWING A NORMAL DELIVERY

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THIS is a case report which deals with the spontaneous rupture of a varix of the left labia majora within two hours following a normal delivery.

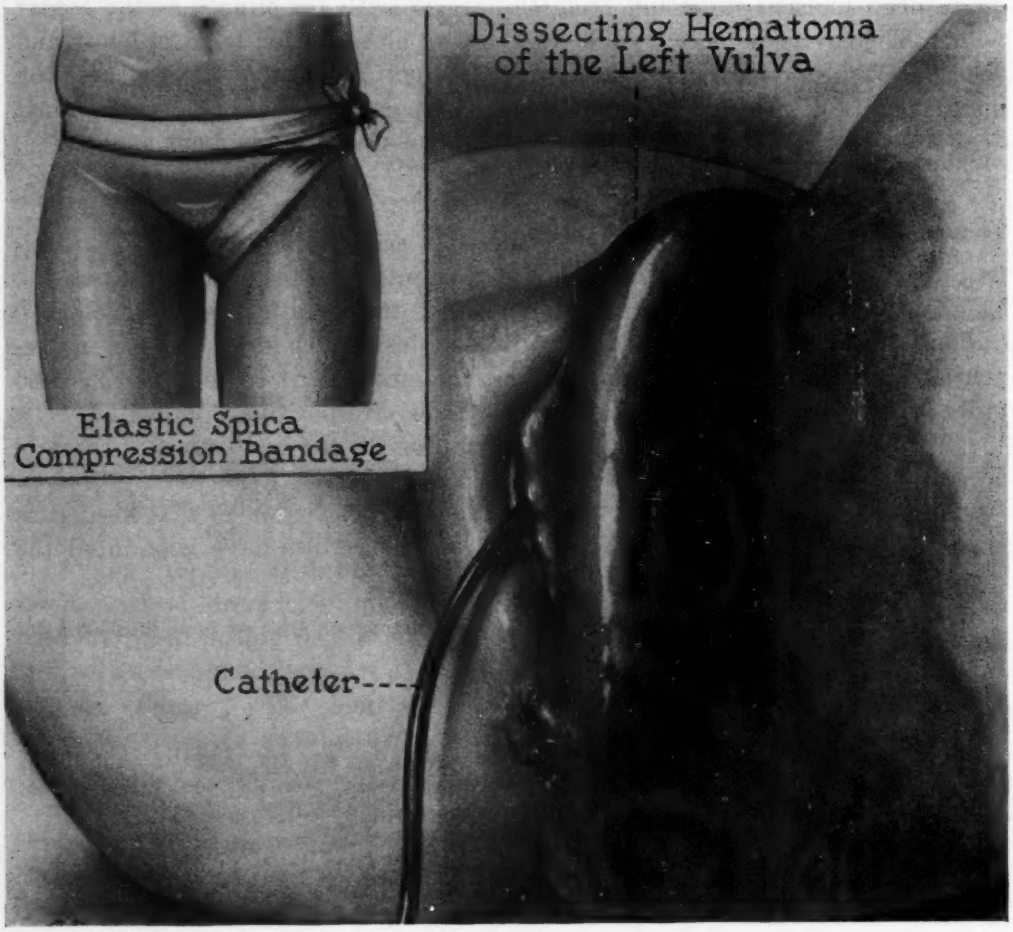

Fig. 1.

Mrs. S. S., white, 25 years of age, gravid i, para o, presented herself because of amenorrhea since Nov. 15, 1949. She was found to be in excellent physical condition and a diagnosis of pregnancy was established. She was about ten weeks pregnant at the initial examination. The Kahn test was negative and she was Rh positive. The pregnancy was essentially uneventful. All laboratory findings of urine and blood were within normal limits.

During the eighth month during an examination of the abdomen, several small varices were noted on the lower abdominal wall. These were isolated and individual on each side of the rectus muscles. She stated that she never before noticed any prominent veins on the abdomen. The labia were checked at the same time and only a suggestive visible vein was noted on the right labia. It was not very large at this examination. However, four weeks later it was a little more pronounced, but completely asymptomatic.

This patient went into labor one week after the computed date and progressed very well so that within six hours with the aid of a left mediolateral episiotomy and prophylactic outlet forceps a baby girl was delivered who weighed 7½ pounds. The placenta came out spontaneously and no excessive bleeding followed. The episiotomy was repaired, the patient was checked, and there were no signs of external bleeding. She was sent to her room. Within two hours after the delivery the intern called that the patient complained of a severe pain in the left labial region. He did not examine her, but ordered a sedative. The pain became excruciatingly severe, so that two hours after the delivery she was examined, and to our surprise we were faced by a huge dissecting hematoma which involved the entire labia majora, the left groin, the left buttocks, and vagina. It blocked the urethra. The mass was tense, shiny, and exquisitely tender, and resembled a huge sausage.

Pressure was necessary to avoid further bleeding. A catheter (Foley) was placed in the urinary bladder to prevent mechanical anuria. Then an elastic spica pressure band was used to compress this hematoma. This stopped further bleeding.

Within five days the hematoma ruptured spontaneously via the mucosal surface of the labial minora vaginal area. The clots were thereafter expressed. This patient made a smooth recovery and left the hospital on the fourteenth day. In six weeks the entire labia and the seat of the rupture of the hematoma were healed.

GRANULOSA-CELL TUMOR OF THE OVARY

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GRANULOSA-cell tumors are rather common, comprising about 10 per cent of all solid ovarian neoplasms (Novak[1]). Of this number from 20 to 30 per cent show clinical evidence of malignancy (Novak,[2] Anderson[3]). The purpose of this paper is to present a case of granulosa-cell tumor with interesting microscopic findings.

A. H., a 48-year-old, white, Italian woman, was admitted to the hospital on Jan. 26, 1950, complaining of a sudden onset of abdominal pain, enlargement of the abdomen, nausea and vomiting. This pain had begun on the evening before. There was no past history of a similar pain. There were no bowel or urinary symptoms. She complained of continuous vaginal spotting for the past six or seven months. Physical examination on admission revealed a tender, rigid abdomen, with an intra-abdominal mass the size of a seven-months' pregnancy. Temperature was 100.2° F. A white blood count revealed 21,300 cells, 95 per cent polymorphonuclear leucocytes and 5 per cent lymphocytes.

On the basis of these findings, a preoperative diagnosis of ovarian cyst with torsion of the pedicle was made.

Pathological Data.—The specimen was that of an ovary and attached tube (Fig. 1). The ovary was an enlarged irregularly circular cystic structure weighing 7,120 grams. It was covered with a thick grayish-white capsule, beneath the surface of which were noted numerous yellowish-brown areas which were quite vascular. The periphery of the tumor was studded with numerous hemorrhagic thin-walled cysts, varying in size from 2.0 to 6.0 cm. The tumor was multiloculated, containing fluid that varied from a bright red serosanguineous fluid to dark liquid blood. The total volume of fluid removed from the tumor measured 900 c.c. Exerting pressure on the external surface of the tumor, one has the sensation of breaking up fibrous septa within the tumor. Cut section of the ovary revealed cystic spaces varying in size from 2 to 7 cm. in diameter. The contents of the cysts for the most part were either old clotted blood or fresh liquid blood and the cysts were limited to the periphery of the tumor. The center of the tumor had a spongy appearance, was of a grayish-red color, with the tissue arranged in a laminated fashion. The Fallopian tube was attached to one portion of the ovary. Its proximal end seemed to merge with the ovarian capsule. The tube was an elongated undulating structure measuring 11 cm. long, and 1.4 cm. in diameter. The fimbriated end of the tube was patent. To the posterior surface of the tube were attached two parovarian cysts measuring 1.5 cm. in diameter. Separately received was an appendix which measured 8.5 by 0.4 cm. Its serosal surface was shiny and glistening with minimal injection of the serosal vessels over its distal third.

Microscopic Description.—The architecture of the ovary was destroyed by a marked cellular infiltration of eosinophilic-staining cells with relatively large hyperchromatic nuclei. The arrangement of cells varied in different parts of the tumor. The cells were arranged in (a) diffuse variety (Fig. 2) with very little connective tissue proliferation; (b) folliculoid patterns where the cells were arranged in rosettes, with central lumina containing eosinophilic material (Call-Exner bodies); (c) cylindromatous and pseudoadenomatous pattern, where there was marked connective proliferation and invasion, breaking up the cell masses into solid and tubular cords (Figs. 3 and 4).

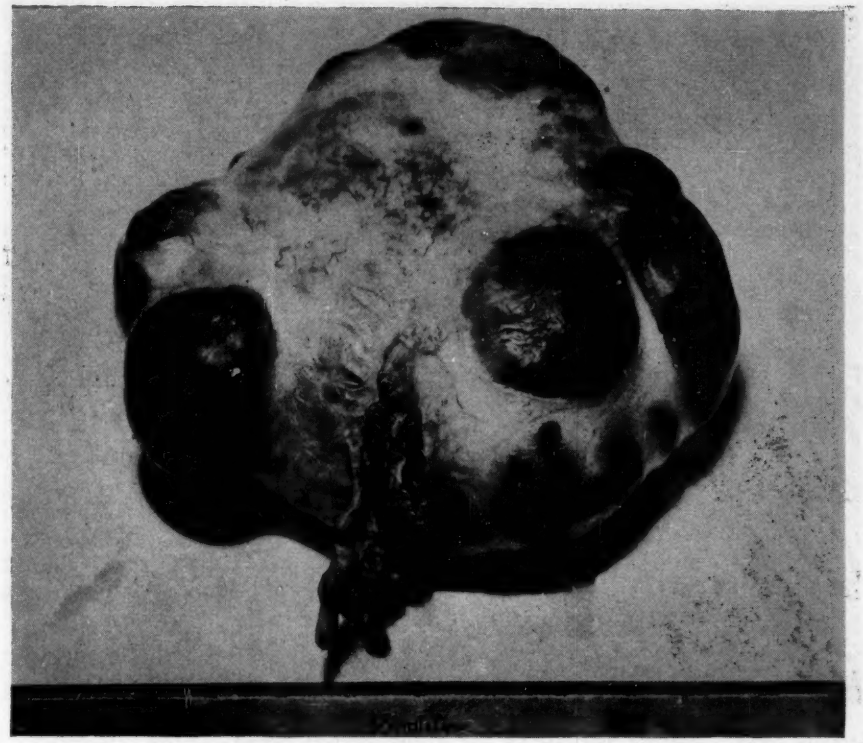

Fig. 1.—External view of granulosa-cell tumor with attached Fallopian tube. (Courtesy of the Armed Forces Institute of Pathology.)

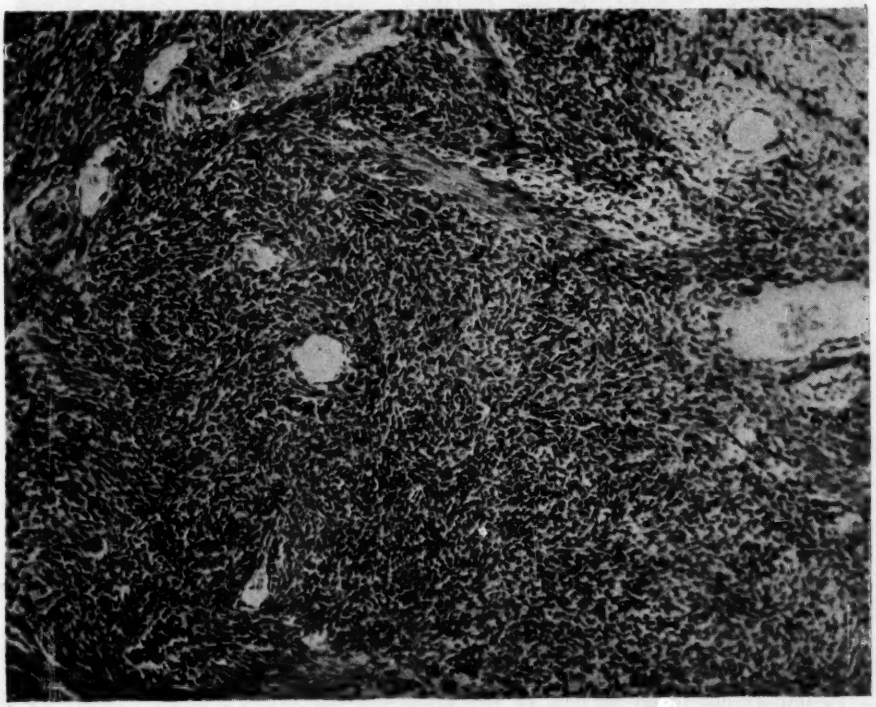

Fig. 2.—The granulosa cells arranged in a diffuse pattern (×75). (Courtesy of the Armed Forces Institute of Pathology.)

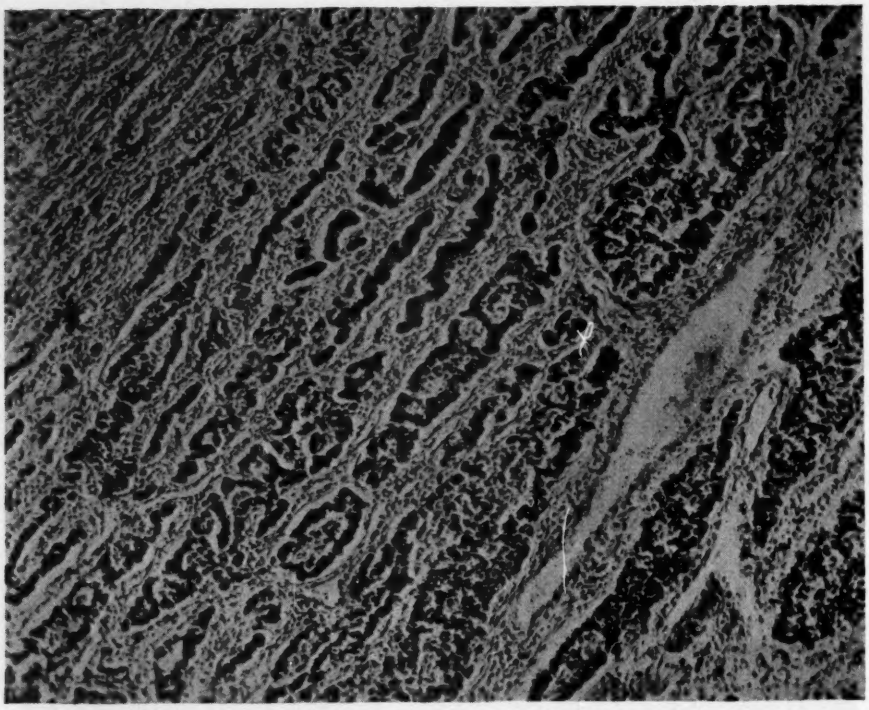

Fig. 3.—The cylindromatous pattern of the granulosa-cell tumor (×75). (Courtesy of the Armed Forces Institute of Pathology.)

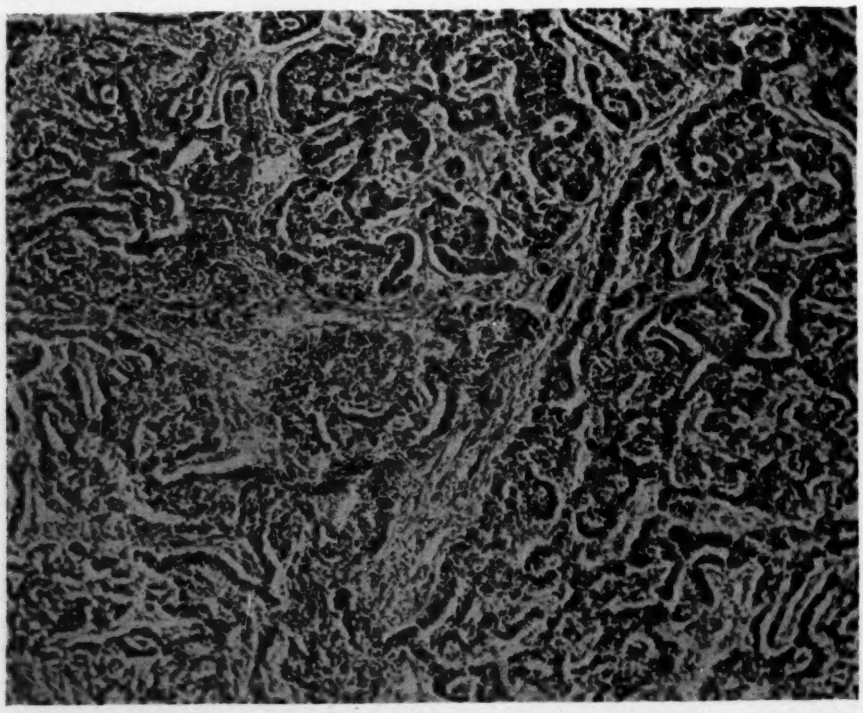

Fig. 4.—Pseudo-adenomatous pattern of the granulosa-cell tumor (×75). (Courtesy of the Armed Forces Institute of Pathology.)

Within the cell masses many mitotic figures were noted per high-power field. A fat stain revealed the presence of numerous fat droplets within the cytoplasm of many of the cells between the granulosa cells. Many areas of hemorrhage and necrosis were scattered throughout the tumor mass.

Sections of the Fallopian tube and the appendix revealed no remarkable changes.

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PERIPHERAL RADICULONEURITIS COMPLICATING PREGNANCY

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REPORTS of the severe fulminating type of peripheral radiculoneuritis complicating pregnancy are not common. The majority of those cases previously reported had evidenced marked and prolonged vomiting in the early stages of the pregnancy, with excessive weakness followed by paralysis of varying degree.[1] Most writers attributed the onset of this type of sickness to a severe vitamin B_1 deficiency.[2, 3, 4] We wish to present a case that gave no history of excessive vomiting, and also did not respond to vitamin B_1 therapy.

Mrs. A. R., a primipara, aged 30 years, was seen for the first time in the third month of her pregnancy. Her only complaint at that time was morning nausea for the preceding two-week period, and this was treated with two successive injections (intramuscular) of equal parts of thiamine and pyridoxine. She did not complain of this feeling again.

Her past history revealed scarlet fever (degree of severity unknown) at age 3, tonsillectomy at 26, plus an operation for "high instep" on her right foot in her ninth year. Menstrual history was negative, previous to the amenorrhea.

Physical examination revealed a short, kyphoscoliotic woman with a moderately contracted pelvis, because of which she was immediately classified as a possible subject for cesarean section. At this time, the patient seemed to have normal gait and posture.

She was placed on therapeutic formula vitamins plus folic acid and on ferrous gluconate therapy. Routine blood count revealed 3,600,000 red blood cells and 12 Gm. hemoglobin.

In the fourth month of pregnancy, she began to notice an excessive weakness in both legs on attempting to climb stairs or to step upon a curb or platform. She neglected to mention this observation immediately, but did complain of "lack of strength" and her blood pressure dropped to 100/70. Another count was taken and the red blood cells had dropped to 3,380,000 with hemoglobin reading the same as previously obtained. Because of this, she was given six injections of a liver-vitamin B complex solution plus three injections of vitamin B_{12} over a six-week period.

The weakness, however, became progressively worse. By the sixth month the arms were involved and her gait was a little uncertain, with numerous falls occurring. At the conclusion of an office visit at this time the patient fell on the threshold of the outer door and sustained severe bruises of both knees. From then on, she was always accompanied and assisted by her husband and/or a sister.

Neurological examination at the sixth month revealed the presence of an impaired, somewhat waddling gait. The patient walked with great effort as though she were using extra energy to drag her legs along. Movement of all extremities seemed somewhat painful to her.

The right facial muscles showed definite weakness when she tried to smile or show her teeth. The right orbicularis oculi muscle was involved, indicating a peripheral type of facial weakness. The handgrips were weak, also the deltoid muscles.

In the lower extremities, the quadriceps group showed definite weakness on both sides; all deep tendon reflexes were absent. Pin-prick sensibility was diminished below knee level; there was loss of position sense of both great toes.

Intensified treatment in the form of daily intramuscular injections of 150 mg. of thiamine chloride was begun. However, the patient objected strenuously, and, after seven injections had been given, this therapy had to be discontinued. Whether this was necessitated by the fact that her husband, previously untrained, was the one who was administering the injections or by the acidity of the material introduced into the tissues is not known.

The neurological symptoms progressed more rapidly so that the patient finally had to be hospitalized. After a six-day "building-up" period in which plasma and blood were administered, hysterotomy with delivery of a viable male baby was accomplished. Both tubes were ligated by the Pomeroy technique, because of the type of pelvis involved and the danger of recurrence of this condition.[5]

Prior to the operation, the patient kept complaining of "things going black" (while lying in bed) and of "spells" where she became quite confused and disoriented.

Immediately on recovery from the anesthesia, the patient seemed to begin improving. The facial weakness disappeared by the fourth postoperative day, so that her smiles equalled those of other patients in the room. Her arms slowly regained strength, and by the sixth day, she was walking about the room holding onto a chair.

Four months later, this patient returned for a check-up visit and surprised all concerned with the statement that she was back at work at her secretarial job. Her gait was good, with the slightest suggestion of waddling. Pin-prick sensibility had increased, but was still not normal. Deep tendon reflexes were improved.

Dystrophy and poliomyelitis were considered, but, because of the type of onset, were discarded. There had been no febrile episodes since pregnancy had intervened. Acute infectious polyneuritis was also considered but the lack of sensory findings, plus the rarely symmetrical and seldom gradual onset in this latter condition made it unlikely.

Summary

This case of peripheral radiculoneuritis complicating pregnancy was relieved by the termination of the pregnancy by cesarean section, with favorable results. The patient did not respond to intensive vitamin therapy, as suggested in previous papers, and had no history of the severe and/or protracted bouts of vomiting that had been reported in this type of case prior to this writing.

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STREPTOMYCIN IN THE THERAPY OF TUBERCULOSIS OF THE FEMALE GENITAL TRACT

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DURING the last year there have been several reports dealing with the results of streptomycin therapy in tuberculosis of the female genitals.[1, 2] Inasmuch as previous reports have dealt with less extensive involvements, it seems advisable to report the following case.

A 19-year-old, single, nulliparous, Mexican girl, hospital No. 49-745, was first seen at the State University Hospital on Jan. 17, 1949, complaining of vaginal discharge and bleeding for six months, and painful inguinal nodes for three years. Both parents were living and well. There were no dead siblings, and no history of tuberculosis in the family or of other exposure. In 1936, she entered a tuberculosis sanatorium because of cervical lymphadenopathy and questionable chest involvement and remained for three years. Unfortunately, a fire destroyed all records of this hospital so that additional information was not available. In 1937, she developed an abscess above the right ankle which drained intermittently for several years. In October, 1945, the patient was sent to another tuberculosis sanatorium where she remained under observation for five months. Pleural thickening was demonstrated but no soft shadows or other evidence of active tuberculous infection was demonstrated. In 1946, a tender painful mass appeared in the right inguinal region. This drained spontaneously and then healed after ultraviolet light therapy. In March, 1948, the patient again noticed swelling in the right inguinal area which subsequently broke down and drained. During the six months prior to admission she developed a bloody purulent vaginal discharge.

Menstrual periods started at the age of sixteen years and were always irregular at three- to six-month intervals. During the six months preceding admission there had been constant vaginal spotting. The patient had felt well and had suffered no pelvic pain or discomfort.

Physical findings revealed a somewhat underdeveloped and undernourished, intelligent, cooperative woman in no distress. Examination revealed (1) scarring of the right side of the neck; (2) a depressed scar on the lateral aspect of the right leg just above the external malleolus; and (3) a large scar in the right inguinal region with small matted residual nodes. The outlet was nulliparous; Bartholin's and Skene's glands were negative. The upper vagina was so constricted as to block passage of the finger tip. Speculum inspection revealed a tag of bleeding granular tissue protruding through this constriction. The uterus was anterior and freely movable. Both adnexa were palpable and normal. A tentative diagnosis of tuberculosis of the vagina and cervix was entertained.

The usual laboratory findings were within normal limits. An x-ray film of the chest showed no disease. Agglutination tests for brucellosis were negative. On Feb. 2, 1949, dilatation of the vagina, curettage of the uterus, and biopsy of the cervix were done. After the constriction of the upper vagina was dilated, the cervix was seen to be replaced by a red granular exophytic lesion involving the entire structure. The cervical canal was dilated and normal-appearing endometrium was removed. Both adnexa were normal on palpation. Histologic examination of the cervical and endometrial tissue revealed intense chronic granulomatous cellulitis with large numbers of closely packed lymphocytes, plasma cells, and large mononuclear leucocytes (Fig. 1). There were focal nests of endothelial cells with many large multinucleated cells resembling Langhans cells. The pathologic report was chronic granulomatous vaginitis, cervicitis, and endometritis characteristic of tuberculosis.

Acid-fast stains of these tissues were negative for tubercle bacilli. Guinea pig inoculations of material removed at the time of curettage were negative. From Feb. 10, 1949, the patient was given 1 Gm. streptomycin intramuscularly in two equal doses daily for eighty-seven days without untoward reaction. Audiograms showed no hearing loss. The patient has had no further vaginal bleeding or discharge.

Fig. 1.

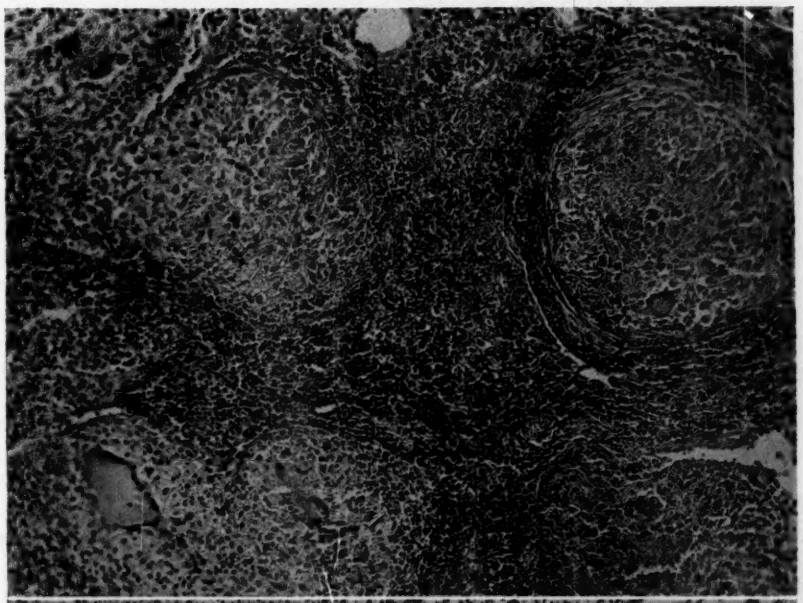

Fig. 2.

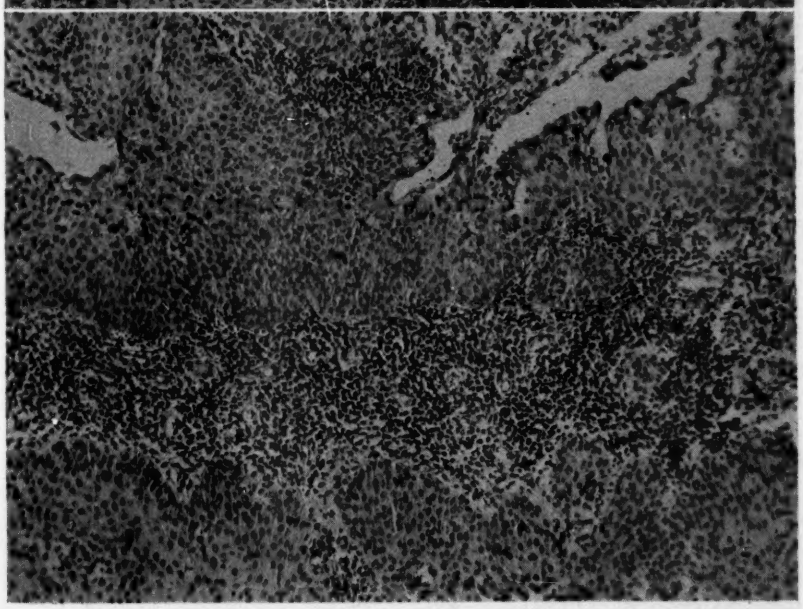

Fig. 1.—Cervical biopsy, February 1949, before therapy. Intense chronic granulomatous cellulitis with large numbers of plasma and large mononuclear cells. There were focal nests of endothelial cells with giant cells typical of tuberculosis.

Fig. 2.—Cervical biopsy, Jan. 26, 1950, one year after therapy was started. The stroma is composed of dense fibrous tissue with some chronic inflammatory cells. In places squamous epithelial cells are developing in mucus-secreting glands.

On May 17, 1949, another uterine curettage was done. The upper vagina was still slightly constricted. The cervix was well epithelized and normal, and there was no evidence of granulation tissue. No tissue was obtained on curettage. However, cervical biopsy showed chronic cervicitis with epidermization but no evidence of tuberculosis. After three months of digital and graduated mechanical dilatation, the constriction of the upper vagina entirely disappeared and a normal well-epithelized cervix was visible.

Fig. 3.

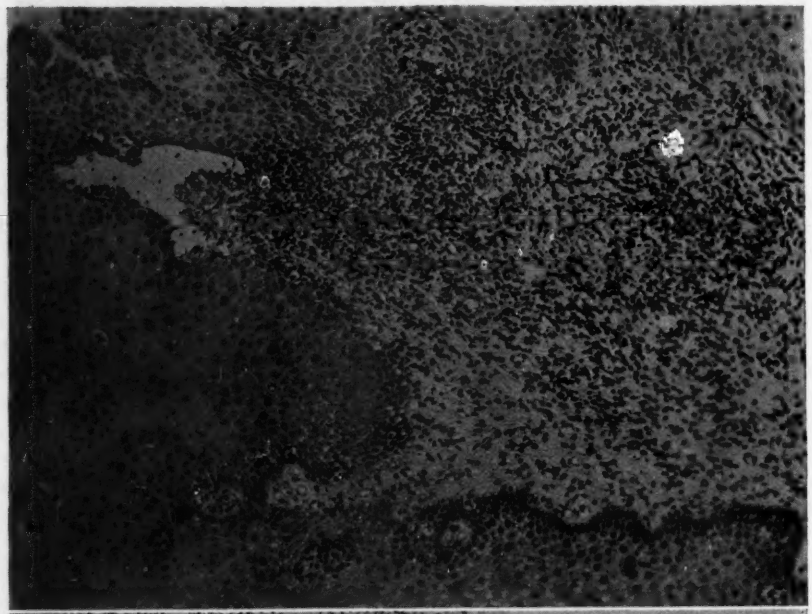

Fig. 4.

Fig. 3.—Cervical biopsy, 17 months after therapy. Acanthotic, hyperplastic stratified squamous epithelium.

Fig. 4.—Endometrium 17 months after therapy. Keratinized squamous epithelium, endometrial glands lined by hyperplastic squamous epithelium.

The patient was concerned because there had been amenorrhea since the cessation of the vaginal spotting and discharge, although she had always menstruated irregularly. In November, 1949, 1 mg. stilbestrol was prescribed daily for twenty-one days and was to be repeated after a ten-day rest period. No vaginal bleeding resulted. However, it was suspected that the medication was not taken because of the nausea produced.

On Jan. 26, 1950, a third uterine curettage and cervical biopsy were done. The vagina was not constricted and pelvic findings were normal. Scant endometrial tissue was obtained (Fig. 2). The pathologic diagnosis was chronic cervicitis with epidermization, and squamous metaplasia of endocervix and endometrium. In February, March, April, and May, 1950, the patient had bleeding episodes of three days' duration. On May 18, 1950, endometrial and cervical biopsies were obtained. The tissues again revealed chronic cervicitis with epidermization and endocervicitis with squamous metaplasia (Figs. 3 and 4). The patient is now working as a diet maid and has no complaints.

Comment

Until recently the usual treatment of female genital tuberculosis was abdominal total hysterectomy with bilateral salpingo-oophorectomy. Unfortunately, many of these patients were in the early twenties and surgical castration often produced troublesome symptoms. With the advent of streptomycin, new hope arose that this antibiotic would arrest or cure gynecologic tuberculosis.

When this patient was placed on streptomycin therapy no reports of its value in such conditions were available. However, during the year Aranson and Dwight[1] reported upon a patient with endometrial tuberculosis apparently successfully treated by the antibiotic, and Sered, Falls, and Zumma[2] published the results of streptomycin therapy on twenty-three patients. The latter authors divided their patients into three groups; the first group was the largest and consisted of patients whose genital tuberculosis was diagnosed preoperatively. These patients were given the drug preoperatively for three to four weeks and received another course of the antibiotic postoperatively. There was clinical improvement prior to surgery, and the technical difficulties encountered in the surgical treatment were markedly reduced. The report does not indicate why these women were subjected to laparotomies following the streptomycin therapy. The second group consisted of a few patients who were treated only with streptomycin therapy following surgery. There were four patients in the third group who responded so well to preliminary streptomycin therapy that surgical intervention was deemed unnecessary.

The patient reported here with extensive vaginal, cervical, endometrial, and probable tubovarian involvement responded so well to antibiotic therapy that after four months there was no histologic evidence of tuberculosis. Conservative management preserved ovarian function as evidenced by the return of menstruation. It remains to be seen if this represents a permanent cure. Regeneration of the endometrium was unusually slow in that on three occasions curettage of the uterine cavity obtained only scant tissue which showed only occasional endometrial glands and stroma while there were many areas of squamous epithelium that appeared hyperplastic, suggesting epithelial replacement of the damaged endometrium.

Summary and Conclusion

A case of extensive vaginal, cervical, and endometrial tuberculosis has been treated sucessfully with streptomycin. This antibiotic is a valuable adjunct to our present armamentarium in thet reatment of tuberculosis of the female genital tract. It is still too early to state whether genital tuberculosis in the female can be cured by such therapy, or whether it should be used only in conjunction with a surgical approach.

This patient has been checked periodically and, as of May 1, 1951, is having regular periods with no evidences of tuberculosis.

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PRECOCIOUS MENSTRUATION ASSOCIATED WITH POLYOSTOTIC FIBROUS DYSPLASIA (ALBRIGHT'S SYNDROME)

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P. G. was first seen May 15, 1948, at the age of 3½ years, because of regular menstruation for three months. Examination showed a child larger than the average for her age. The head showed prominence of both temporal regions. There was a slight pubic hair growth. A right ovarian cyst was found by rectal examination. She was not seen again until Oct. 13, 1949. Her mother stated that the menses had been regular, lasting two or three days. Examination at this time showed a child much larger than one would expect for this age. There was an increased thickening of both temporal regions, making the head almost square. The patient was very conscious of her condition, making examination very difficult. There was a slight proptosis of the right eye. The breasts were enlarged (Fig. 1). The axillary hair had developed. The pubic hair was abundant. The hair configuration was of the female type. The skin of the back showed three areas of pigmentation. The clitoris was small. Rectal examination at this time showed the presence of a right ovarian cyst as at the previous examination. The patient was operated on Nov. 26, 1949. A cyst of the right ovary measuring 10 by 12 by 6 cm. was found. The other ovary was normal. A right oophorectomy was done and an incidental appendectomy. The patient made an uneventful recovery and was discharged Dec. 3, 1949. She was examined again on Jan. 25, 1950, at which time her personality and secondary sexual characteristics had reverted to that of a normal girl of her age. There was no hair on the pubis or in the axillae. There had been no menstruation since the operation. There was no change in the appearance of the head. The patient was checked again on June 1, 1950. At this time there had been no reappearance of menstruation. The pubis and axillae were devoid of hair. The breasts had receded and appeared normal.

Fig. 1.

This case suggested, from clinical evaluation, the presence of a granulosa-cell tumor.

Pathologic Report (Dr. A. E. Lubchenco).—The ovary was subtotally replaced by a unilocular cyst which presented prominent trabeculations but no papillary excrescences. Granulosa-cell tumor was not detected in any of the sections.

The large ovarian cyst was lined by corpus-luteum type of cells showing varying degrees of regression. There were prominent primordial follicles within the wall of the cyst showing atrophy in the thinner portions. Cancerous change or definite granulosa-cell type of lesion was not detected in multiple sections. There were occasional Graafian follicles which showed evidence of maturing.

Diagnosis: Cyst, ovarian, corpus luteal in origin.

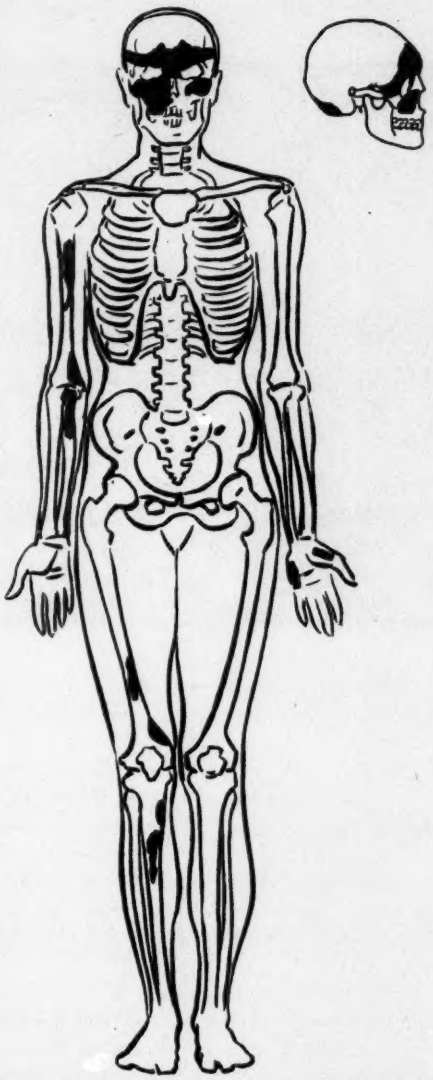

Fig. 2.—Showing bone involvement which is chiefly right sided.

The slides were also sent to Dr. Emil Novak who reported the following: "On examining these sections, I see no evidence of any granulosa-cell tumor or any other neoplastic structures. There are a number of partly maturing follicles with active looking granulosa and the small cyst which you describe, evidently of simple follicular type."

Laboratory Findings: Blood calcium 11 mg. per cent; control 11 mg. per cent; blood phosphorous 7.7 (King Armstrong units), control 4.9 (King Armstrong units), alkaline phosphatase 54 (King Armstrong units), control 10 (King Armstrong units), basal metabolism rate plus 9.

X-Ray Report (T. J. K.) (Fig. 2): Appendicular skeleton: Fibrous dysplasia involving the entire diaphysis of the right humerus and proximal right ulna. Less marked fibrous dysplasia of the proximal half of the diaphysis of the right tibia, and distal third of the diaphysis of the right femur. Also early changes involving the entire shaft of the left fifth metacarpal and the distal half of the shaft of the left first metacarpal. There were also two small cystoid areas in the mid left ilium superior to the acetabulum and a small cystoid area involving a like region of the right ilium. These were not considered clinically significant since small cystoid areas are frequently found here in the young skeleton.

Fig. 3.

Estimated bone age after study of ossification of the wrists and hands was that of a girl between 8 and 9 years.

Roentgen survey of the skull revealed definite osteomatoid sclerotic thickening involving the anterior and middle cranial fossae, and also the inner table of the occipital bone above the foramen magnum (Fig. 3). The bone thickening involved the orbital plate of both frontal bones, lesser wings of the sphenoid bones, with less marked thickening of the greater wings of the sphenoid bones. Both malar bones were also involved, especially the right. The thickening encroached markedly upon the ethmoid paranasal sinuses, and also the cribiform plate of the ethmoid bone. These findings are very typical of fibrous dysplasia.

In view of the skeletal maturity as evidenced by bone age of 8 or 9 years compared with a chronological age of 4 years, plus the fairly extensive polyostotic fibrous dysplasia involving both the appendicular and axial skeletons, we believe that this case of polyostotic fibrous dysplasia fits well into the syndrome described by Fuller Albright, and known popularly as Albright's disease or syndrome.

Comment

The disease is self-limited in that it tends to diminish in activity as the patient grows older. The affected bones do not return to normal, but the lesion may become stationary and no new lesions appear. There is no known specific treatment. Symptomatic treatment is limited to care of any fracture. Aluminum acetate has been suggested because of its effect on the phosphatase enzyme activity. The disease results in shorter stature because of early union of the epiphyses.

Summary

1. A case of precocious puberty due to Albright's syndrome is reported.

2. Unexplained cases of precocious puberty in girls should be thoroughly investigated by complete roentgen study of the skeleton.

3. The cause of precocious puberty and secondary sexual characteristics in Albright's syndrome probably rests in the ovary.

APLASTIC ANEMIA COMPLICATING PREGNANCY*

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IDIOPATHIC aplastic anemia occurring as a complication of pregnancy is rare and the literature contains so few such reports that no fixed opinion as to the best method of treatment has been formulated. The question of whether or not immediate termination of the pregnancy is indicated as soon as the diagnosis is made can be answered only when a sufficient number of isolated cases have been made available for analysis.

Mrs. C. S., a 24-year-old white primigravida, was first seen in the prenatal clinic of the United States Naval Hospital, Portsmouth, Va., on June 25, 1947, in the twenty-sixth week of pregnancy. She stated that she had felt very well since becoming pregnant and had no complaints; she had not previously consulted any physician in her pregnancy. Past history revealed measles, mumps, and a tonsillectomy in childhood, no other illness nor operation. Onset of menstruation at 13 years of age, regular 28-day cycle, flow of 3 days' duration; last menstrual period Dec. 24, 1946. Physical examination was entirely within normal limits, with the uterus enlarged to the size of a twenty-six weeks' gestation. The chest x-ray was normal, blood Kahn test negative, blood type A, Rh factor positive, red blood count 4,760,000, hemoglobin 13.5 Gm., urinalysis normal. Routine prenatal care was instituted and the patient was instructed to return in four weeks.

On July 25 (thirty weeks of gestation) a one plus pedal edema was noted, urinalysis was normal, blood pressure 100/54. A low sodium chloride diet was prescribed together with ammonium chloride, 8 Gm. daily for three days, and she was instructed to return in one week.

At the next visit, August 8 (32 weeks of gestation) the trace of pedal edema was still present, complexion appeared somewhat sallow, and there were several small asymptomatic purpuric spots on the right calf; the patient could not recall having bruised herself in any way. Blood pressure was 110/60, pulse 84, urinalysis normal, a tourniquet test showed normal capillary fragility. Blood studies revealed the following: red blood cells 3,470,000, hemoglobin 10 Gm., platelets 83,000, white blood cells 3,500, with normal distribution in the differential count, bleeding time one minute forty-five seconds, clotting time three minutes. The patient was placed on increasing daily amounts of liver extract, iron, and multiple vitamins and referred to the abnormal obstetrical clinic for further study of the thrombocytopenia and leucopenia.

During the next four weeks she was symptom free, the purpuric spots faded, and no new ones appeared. Further blood studies were made with the following findings: reticulocyte count 3 per cent, color index 1.1, volume index 1.2, hematocrit 30 per cent, prothrombin time 135 per cent, red cell fragility normal, capillary fragility normal.

On September 19 (38 weeks of gestation) a profound change was noted in her condition; pallor was marked, mucous membranes were pale, the pulse rate was 110. She complained of marked fatigability, palpitation, giddiness, a tendency to bruise easily, and bleeding from the gums. Further questioning revealed that she was a graduate nurse although she had done no nursing for several years, there had been no contact with any type of radiation or noxious agent, no drugs had been taken other than the medication prescribed in the clinic (liver extract, iron, vitamins, and ammonium chloride), and there was no evidence of any abnormal bleeding tendency in either her or her family's past history. She was immediately admitted to the hospital for study and therapy.

*The opinions expressed herein are those of the authors and do not necessarily represent those of the Naval Service as a whole.

On admission the patient appeared pallid but otherwise not acutely ill. Blood pressure was 110/70, pulse 100, respirations 24, temperature 99.4° F. The skin was of normal texture but pale and there were several small purpuric spots on the left forearm. Eyegrounds were normal except for retinal pallor. A few small discrete lymph nodes were palpable in the anterior cervical chain but there was no generalized adenopathy. Neither the liver nor spleen was palpable. The uterus was enlarged to the size of a 38 weeks' gestation with the fetus lying in a right occiput anterior position. Fetal heart tones were clear and regular. A one plus dependent edema was present. Laboratory studies at the time were as follows: red blood cells 1,770,000, hemoglobin below 7.5 Gm., hematocrit 16 per cent, white blood cells 4,700, with 2 band forms, 44 segmented forms, and 54 lymphocytes, reticulocyte count 0.05 per cent, icteric index 8, clot retraction very poor, blood sedimentation rate 31 mm. per hour, total serum proteins 5.8 mg. per cent, albumin-globulin ratio 1.32/1.0, cephalin flocculation negative, gastric analysis, no free hydrochloric acid and 18 total acids, urinalysis normal. A sternal puncture was performed and the marrow reported as showing a depression of all elements, the picture being consistent with a diagnosis of aplastic anemia.

Therapy consisted of multiple whole blood transfusions, high protein-carbohydrate-vitamin diet, liver extract, iron, yellow bone marrow capsules, and intramuscular Pentonucleotide. The blood count rose and she felt greatly improved; on September 29, ten days after admission, she entered labor spontaneously at term. At this time the red blood count was 3,050,000, hemoglobin 10.0 grams. One thousand c.c. of whole blood were crossmatched and made available for immediate use.

The course of labor was uneventful and after fifteen hours she was delivered with low forceps through a mediolateral episiotomy of a living male infant, with open-drop ether anesthesia. The infant weighed 6 pounds, 15 ounces, breathed and cried spontaneously, and appeared normal. The third stage was normal with an estimated blood loss of 300 c.c. A whole-blood transfusion of 500 c.c. was given and the patient appeared to be in excellent condition.

Following delivery all therapy was continued and for the first five days she was afebrile, the lochia normal, breasts engorged, corpus involuting well, red blood count 3,600,000. On the sixth postpartum day she became febrile, the temperature rising and falling in a septic manner thereafter to a daily high of 105° F. Physical examination revealed slight vaginal bleeding and a uterus slightly larger than expected for the puerperium. Lochial culture and blood culture were negative. Penicillin and streptomycin were given in therapeutic and later massive doses without any noticeable effect on the septic course. The vaginal bleeding gradually increased and occult blood was present in the gastric content and in the stools. The red blood count showed a gradual fall and 500 c.c. of whole blood were required approximately every 48 hours to maintain the count above three million.

The uterine bleeding continued and on the seventeenth postpartum day the uterus was explored digitally and with a curette. No tissue was found, and the cavity was packed with gauze. Blood continued to ooze about the pack and bleeding recurred upon its removal twenty-four hours later. By the twenty-seventh postpartum day the loss of blood per vaginam was faster than replacement could be made. It was felt that a rapid supravaginal hysterectomy should be attempted as a last resort measure and on October 26, the twenty-seventh postpartum day, this was performed. The procedure was complicated by the edema and friability of all of the pelvic tissues which caused ligatures to cut out but was accomplished in a short period of time; the patient withstood the operation well although her condition was critical at the time despite massive infusions of whole blood.

Grossly the uterus was about twice normal size, pale in color, and showed a spongy edema of the musculature. Microscopic sections revealed subinvolution and edema of the myometrium, the endometrium was scanty, and the glands in an early proliferative phase.

Following the surgery the patient responded well for about forty-eight hours although the temperature continued its daily rise to 105° F. On the third postoperative day she began to bleed profusely from the nose, mouth, and gastrointestinal tract, and died on the fourth postoperative day with clinical findings of myocardial failure and pulmonary edema.

At autopsy the following pertinent findings were recorded: multiple ecchymotic spots diffusely spread over the entire body; petechial and ecchymotic hemorrhages of all visceral and parietal surfaces; edema of the lungs; adhesive peritonitis at the site of the recent pelvic surgery; hemorrhagic gastroenterocolitis; enlargement of the aortic, mesenteric, and lumbar lymph nodes. The liver appeared normal grossly and on its cut surface. The spleen was moderately enlarged, weight 233 grams, color deep red; its cut surface appeared normal except for congestion. Microscopic sections of vertebral body and rib marrow showed marked hypoplasia with an increase of fatty tissue, and a great increase in the number of plasma and reticulohistiocytic cells. There appeared to be a greater depression of the myeloid than of the erythroid elements.

Pathological diagnosis: Aplastic anemia.

The infant was discharged from the hospital at 1 month of age, weight 9 pounds, 1 ounce, physical examination including blood studies entirely normal.

SPONTANEOUS EVISCERATION THROUGH VAGINAL ENTEROCELE

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(From the Hollywood Presbyterian Hospital)

MRS. G. W., aged 59 years, was first seen by F. W. K. on Oct. 11, 1948, with complaints of difficulty in expelling stools and of a bearing-down sensation in the rectum.

Pertinent points in her past history are as follows: Married 33 years, no pregnancies. Appendectomy at age 35, followed by radium treatment for uterine fibromyomas two years later. No vaginal bleeding since radium. In June, 1944, Dr. Heaney operated upon the patient at Presbyterian Hospital, Chicago, doing a urethroplasty, vaginal hysterectomy, and anterior and posterior colpoperineorrhaphy, from which she apparently made an uncomplicated recovery. In 1945 the patient began to notice a bulging from the vagina and she was treated first by insertion of tampons and subsequently by a doughnut pessary. In September, 1948, she had been urged to have a vaginal plastic, but declined.

When she was first seen, general physical examination was essentially negative except for the vaginal condition. She was wearing a large rubber doughnut pessary. Removal of this revealed a very large rectocele and enterocele, with marked peristalsis visible as low as the vaginal introitus. It was noticed that the posterior vaginal wall was exceedingly thin. The anterior vaginal wall and vaginal vault were well supported. Surgical repair was again urged but the patient preferred to remain on pessary treatment. She returned at sufficiently frequent intervals for removal, cleansing, and reinsertion of the pessary. At no time was any evidence of trauma noted.

The patient had no unusual complaints until Jan. 26, 1949. On that day she took an enema and was expelling it when she was summoned to the telephone. Rising from the stool quickly, she felt something between her legs, heard bubbling like gas passing, and upon looking she saw intestines hanging nearly to the floor. After some contemplation she called to state "something has just happened" and she thought she should go to the hospital. She was advised to go to bed and was seen immediately.

Lying comfortably in bed, completely at ease, and in no apparent distress, her appearance belied the difficulties in which she was found. Removal of the bed covers revealed approximately 60 cm. of small intestine lying between her thighs. Pulse was 88 and blood pressure 164/100. There was no evidence of shock. No attempt at reduction was made and the patient was promptly hospitalized.

Two hours after the evisceration the patient was taken to the operating room, and under nitrous oxide and oxygen anesthesia the perineum and vulva were thoroughly but gently cleansed with soap, water and saline. The exposed bowel was cleansed with saline only. No further preparation was done. The bowel appeared to be in good condition and was replaced within the pelvis by means of a sponge forceps through the transverse rent, 6 cm. in length, in the posterior vaginal wall at the introitus. Penicillin and dihydrostreptomycin were placed in the pelvis and the rent closed with interrupted mattress sutures of No. 1 chromic catgut.

A vaginal pack was inserted and the patient returned to bed in good condition. Temperature following surgery was 100.2° F. Penicillin and intravenous glucose and saline were continued. The day following surgery peristalsis was active and the patient was drinking freely. Temperature was normal by the fourth postoperative day. Convalesence was rapid and uneventful. Granulation was minimal in amount and responded promptly to silver nitrate. Vaginal packing was maintained for support and was changed at frequent intervals. When healed the rent was approximately 3 cm. in length.

On March 30, 1949, the patient was operated upon for the enterocele by Dr. Heaney. His findings and procedure are contained in the following note:

"I remember this patient very well and I clearly recall the operation which I did in June, 1944. Though she had never had a child she had a marked urethrocele, cystocele, descensus of a fibroid uterus and rectocele. The pelvic tissues were all very thin. At that time the patient had no enterocele. The operation presented no unusual difficulties and her recovery was uneventful. Now the posterior vaginal wall is extremely thin and active peristalsis can be seen in the enterocele.

"A transverse incision was made at the introitus at the mucocutaneous junction. The enterocele was immediately entered and free loops of small intestine filled the immense enterocele. The small intestines were pushed up into the pelvis and held back by a small gauze pack. The entire posterior vaginal wall was extremely thin and consisted only of vaginal mucosa and the peritoneum of the enterocele firmly adherent to one another. The patient's husband is impotent and she placed no importance upon a functional vagina.

"The entire posterior vaginal wall was removed, laterally to the edges of the retracted levator muscles, and upward to the vaginal vault. The posterior wall of the enterocele came down to the introitus and covered the rectum and the sulcus on each side and could not be removed from its attachments. The sacro-uterine ligament on each side was isolated and a strip of peritoneum about an inch wide was removed with difficulty from the surface of the rectum and its sulci, from the sacro-uterine ligament on one side to the opposite side. A No. 2 chromic running catgut suture was passed picking up first the left sacro-uterine ligament, then stitching the anterior peritoneum to the rawed edge of the posterior peritoneum in an over and over stitch up to the right sacro-uterine ligament around which the suture was placed. Then the ends of the suture were drawn together and tied, thus bringing the sacro-uterines together in the midline. A finger was inserted into the rectum to see what effect this suture had on the caliber of the bowel. The tightening was insignificant, so a second suture was placed in a similar way resuturing the sacro-uterines together and picking up the rawed strip of peritoneum. Then an interruped No. 2 chromic suture was passed first through the left edge of the vaginal mucosa, then through the fascia of the left levator ani, then through the edge of the right vaginal flap. Similar sutures were placed from the vaginal vault down to the introitus. Black silk sutures were used for the perineum. The resulting posterior wall seemed very strong. The vaginal canal admitted one finger and was one finger deep.

"Convalesence was uneventful. Great care was used postoperatively to prevent a fecal impaction. The etiology of the enterocele is only conjectural. I have never heard or read of a spontaneous rupture of an enterocele before."

When she was seen on May, 3, 1949, healing was complete and the patient felt well except for symptoms of a mild cystitis which promptly disappeared with an increase in her fluid intake. The vagina would admit one finger to a depth of 4 cm. The anterior and posterior segments were well supported. Her most recent examination on Sept. 26, 1949, revealed her pelvic situation unchanged except that the vaginal canal now admits a finger to a depth of 5 cm. She is able to carry on her usual household duties.

We have been unable to find any references to this condition in the literature. Extensive inquiries have also been unsuccessful.

Summary

1. A case is presented of a spontaneous evisceration through a rent in an enterocele subsequent to a vaginal hysterectomy and vaginal plastic four years previously.

2. Immediate replacement of the intestine through a rent with repair was followed by an uneventful recovery.

3. Secondary repair of the enterocele yielded a good result.

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THE FROG TEST FOR CHORIONEPITHELIOMA

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IN 1948 workers in Ohio[1, 2, 3] reported the use of the male frog (*Rana pipiens*) as an accurate, rapid, simple, and sensitive test for pregnancy or retained living placental tissue. This test is based on the principle that when stimulated with gonadotropic hormone, even in very small amounts, the male *Rana pipiens* puts out readily recognizable sperm in the urine. Although one would expect that the test would be positive in chorionepithelioma, no report has been found in the literature confirming this expectation. This report is to record the clinically substantiated fact that the frog test is of value in chorionepithelioma and is of special value to the physician responsible for the care of such a patient because the test is inexpensive, information is obtained speedily (four hours), and the test is accurate, apparently reflecting changes in the gametokinetic hormone with approximately the same accuracy as the more classical Friedman or Aschheim-Zondek tests.

The rationale of using the frog test is this: Wilson and associates,[4] in work in which they made quantitative determination of the chorionic serum gonadotropin, believe that the fluctuating level of the hormone is the result of changes in the rate of production during pregnancy and that the Langhans cells are the producers of the hormone. They report a direct proportion between the rate of excretion (therefore the rate of production) of chorionic serum gonadotropin and the number of Langhans cells. It is our belief that Wilson's gonadotropic hormone and Miller's gametokinetic hormone are different names for the same substance.

Crossen[5] expresses the common belief that chorionepitheliomas arise from fetal cells covering the chorionic villi and pathologists are almost unanimous in saying that Langhans cells are always found in malignant chorionepitheliomas. It is also pointed out that the more malignant the growth the greater the percentage of Langhans cells. For these reasons the frog test should be positive in cases of chorionepitheliomas.

In support of this conclusion is the case of an 18-year-old girl whose full-term pregnancy terminated in a stillbirth two and one-half months prior to her admission to this hospital. Bleeding was the cause of her admission and tissue removed from the uterus was diagnosed by the pathologist as chorionepithelioma malignum and in the absence of any discoverable signs of metastases a total hysterectomy was done. Recovery from surgery was rapid and uneventful and the patient still (260 days postoperatively) shows no signs of recurrence or metastatic growth. The surgical specimen was an infiltrating growth in the uterus and consisted of highly anaplastic cells. There were large areas of hemorrhage and necrosis. The cellular elements were both syncytial and Langhans cells. The latter were frequently multinucleated. Mitotic figures were present. There were some inflammatory changes about the areas of advancing tumor. The tumor extended deeply into the myometrial tissue.

Frog tests were always run on at least two animals and there were never conflicting results. Friedman tests were run as checks on the frogs, and the urine used was from the same specimen.

The preoperative tests were strongly positive in 30 minutes. The postoperative frog tests remained positive until the eighth day when they first became negative. After the first three days the test became progressively less strongly positive. The Friedman first became negative on the twelfth day. Since that time all tests have remained negative.

In conclusion it is felt that the frog test is valuable in cases of chorionepithelioma for it gives a rapid, inexpensive, dependable, sensitive, and simple test to aid in diagnosis and prognosis.

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Erratum

In the article, "Oxygen Saturation of the Blood of the Newborn, as Affected by Maternal Anesthetic Agents," by E. Stewart Taylor, Clifton D. Govan, and William C. Scott, in the April issue of the JOURNAL, on page 851, the last sentence of the first paragraph under the heading "Conclusions" should read, "Furthermore, no infants required resuscitation after regional anesthesia as compared with from 10 to 60 per cent who did following the various general anesthesias."

Department of Reviews and Abstracts

Selected Abstracts

Labor, Management, Complications

Weiner, Albert E., and Reid, Duncan E.: The Pathogenesis of Amniotic-Fluid Embolism. III. Coagulant Activity of Amniotic Fluid, New England J. Med. 243: 597, 1950.

Again in the same journal under the title of "The Pathogenesis of Amniotic-Fluid Embolism," by Dr. Albert E. Weiner and Dr. Duncan E. Reid, of the Department of Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital, comes this report on the coagulant activity of amniotic fluid. They precede their case report by a review of 22 known cases (both published and unpublished) of amniotic-fluid embolism.

These case reports revealed that 7 patients died suddenly in a state of shock in delivery. However, of the remaining 15 who survived delivery, 13 had hemorrhagic manifestations prior to death. Nine patients experienced postpartum hemorrhage. One patient had major bleeding from the mouth. Another showed ecchymoses and extravasation of blood in the abdomen and at the root of the mesentery, and 2 died from ruptured uteri with uncontrollable hemorrhage.

The authors report in detail the case of a 27-year-old gravida iii, para 0, overdue two weeks, whose membranes ruptured spontaneously, and 8 hours later labor started. One and one-half hours after the onset of labor a diagnosis of premature separation of the placenta (nontoxic variety) was made. Within 30 minutes a rapid cesarean was performed. At operation a dead fetus was found together with a completely separated placenta. At the beginning of the operation the patient began bleeding from the mouth and gums. A transfusion of 500 c.c. of blood was given. One hour following the cesarean, because of continued bleeding, a supracervical hysterectomy was performed, preceded by 2,500 c.c. of freshly drawn blood. The patient went into profound shock with deep cyanosis when the abdomen was reopened. At reoperation there were extensive intraperitoneal and retroperitoneal hemorrhages. The patient died 1½ hours after hysterectomy in spite of substantial blood replacement. Gross examination of the lungs was not striking. On microscopical examination squamous cells and masses of mucus and fat globules were found in many of the small vessels throughout the lungs.

A review of the hemorrhagic tendencies in this case led to a study of the possible effect of amniotic fluid on the coagulation of the blood. Studies on amniotic fluid have shown that it contains a marked coagulant activity. The factor is similar to thromboplastin in its behavior, and it is entirely inactivated by small amounts of heparin in vitro.

It is suggested that amniotic fluid normally plays a role in coagulation of intrauterine blood and that this assists in postpartum hemostasis. However, amniotic fluid may, on occasion, gain entrance into the maternal circulation, producing intravascular clotting. If this should occur, fibrinogen would be consumed, and the local situation in the uterus would lead to postpartum hemorrhage because of failure of the blood to clot normally, as the result of defibrination.

As to the treatment of this syndrome of cyanosis with sudden shock during labor or at delivery, no specific therapy has been advocated. They suggest that heparin, 50 to 75 mg. administered intravenously, might be effective in decreasing the clotting activity of the amniotic fluid that had escaped into the maternal vascular system.

Should the patient rally from the initial shock, hemorrhagic manifestations may develop within minutes to one or two hours of delivery. One should consider that a state of afibrinogenemia exists as the basis of these changes. A few cubic centimeters of the patient's venous blood should be drawn to determine the clot size and stability. From observations on other conditions in which maternal afibrinogenemia has developed, the clotting mechanism should be restored by the administration of adequate amounts of fibrinogen (4 to 6 Gm.). This therapy should be accompanied by transfusions sufficient to replace blood loss.

Mallory states that from a prophylactic standpoint it seems logical not to induce violent labor by Pituitrin and to prevent it if possible in elderly primiparas, particularly those who have had a premature rupture of the membranes. JAMES P. MARR.

Kaiser, Irwin H.: The Effect of Epinephrine and Norepinephrine on the Contractions of the Human Uterus in Labor, Surg., Gynec. & Obst. **90**: 649, 1950.

In a previous study, Kaiser reported that Adrenalin in small dosage produced a temporary inhibition of uterine contractions in women in labor, followed by a breakthrough, and then, after cessation of therapy, a short period of stimulation of contractions. These effects were not seen in every patient. In this present study, the author now reports the use of continuous, intravenous, high dilution levoepinephrine and levonorepinephrine in pregnant patients during labor. Levoepinephrine caused a short inhibition of contractions followed by partial recovery approximately 15 minutes after the start of the intravenous drip. After the discontinuance of the drip, uterine activity returned to normal and in a few minutes there appeared an increase in tone, force, and frequency of the contractions. This lasted about 5 minutes. In the patients receiving levonorepinephrine there was an immediate transitory rise in uterine tone. There was also an increase in frequency of the contractions but no apparent increase in force. In a few instances there was marked increase in the contractile activity of the lower uterine segment.

Inasmuch as norepinephrine increases the systolic and diastolic pressure proportionately and causes vasoconstriction without increased cardiac output, it has been found to be an ideal drug in both surgical and anesthetic shock. The author, however, cautions against its use in pregnancy because of its effect on the uterus with possible onset of labor or damage to the baby. LOUIS M. HELLMAN.

Hellman, Louis M., Harris, Jerome, and Reynolds, S. R. M.: Characteristics of the Gradients of Uterine Contractility During the First Stage of True Labor, Bull. Johns Hopkins Hosp. **86**: April, 1950.

This is another paper by the Baltimore group headed by Reynolds, on the physiological characteristics of uterine contractility as determined by the multichannel strain-gage tokodynamometer. For this paper 151 normal women were studied. The results of these studies have been tabulated on punch cards and information derived regarding the characteristics of contractility during the first stage of labor.

Sixty-eight primiparas and eighty-three multiparas comprised the group of patients. Six hundred seventy-seven separated 20-minute periods of observation were made on these patients. A decreasing gradient of activity was found from the fundus to the lower uterine segment in both multiparas and primiparas. Thus, the fundus contracted more strongly and had a contraction of greater duration and greater efficiency than the mid-uterus or lower uterine segment throughout labor.

The increment of fundal dominance increased throughout labor both in multiparas and primiparas but more so in the latter than in the former. The percentage increase in primiparas was 41.5 per cent while that in multiparas was 60.1 per cent. The greatest increase in fundal dominance occurred in multiparas after the cervix was dilated about 5 cm. Such an increase after 50 per cent dilatation of the cervix was not observed in primiparous women. L. M. HELLMAN.

Parviainen, Sakari, and Ingman, Ove: Protracted Labor, Acta obst. et gynec. Scandinav. **30**: Supp. 7, 87, 1950.

The material of the First Women's Clinic of the University of Helsinki was analyzed with the object of achieving a working definition of prolonged labor, and of clarifying its principal causes. When patients with various complications were excluded, there remained, during the period 1946-1947, a series of 5,259 presumedly "normal" parturients whose term-sized fetuses were in occiput anterior positions. These patients constituted 77.3 per cent of all women delivered during the year considered; 2,444, or 44.47 per cent, of them were primigravid. Parviainen and Ingman suggest that labor be defined as prolonged beginning 24 hours from the onset of regular uterine contractions at 10-minute intervals or less. By these criteria, labor was prolonged in 7.39 per cent of these women. The incidence of prolonged labor during the period 1945-1947 was 6.75 per cent; the prolongation occurred in 642 of a total of 9,513 labors, of which only 104, or 16.2 per cent, were in multigravidas. These figures corroborate the often-reported preponderance of prolonged labor in primigravidas. In this two-year series, there were 9 fetal deaths from various causes (fetal mortality: 0.17 per cent), and one maternal death from infection in a patient with a neglected labor seen terminally for the first time (maternal mortality 0.16 per cent).

The same material was analyzed for the years 1935-1947, and the commonest causes of prolonged labor listed. These were: uterine inertia (present to some degree in 85 per cent), maternal exhaustion, late rupture of membranes, and disproportion due to various causes. It is suggested that timely artificial rupture of membranes may often have a beneficial effect on the termination of prolonged labor, since 47 per cent of patients having such labor were delivered within 2 hours following amniotomy. DOUGLAS M. HAYNES.

Menstruation

Givens, William P., Gause, Ralph W., and Douglas, R. Gordon: Rational Therapy for Secondary Amenorrhea, New England J. Med. **243**: 357, 1950.

From the Woman's Clinic of the New York Hospital and the Department of Obstetrics and Gynecology, Cornell University Medical College, appears this study.

The purpose of this study is to evaluate 50 patients treated for secondary amenorrhea in an attempt to draw certain conclusions regarding the production of ovulation and subsequent pregnancy. They clearly state that simple substitution therapy in the treatment of menstrual disorders is not adequate therapy and that every effort must be made to stimulate the ovary or eradicate the factors that depress it.

In general, these factors can be classified into four groups: anatomic defects causing obstruction; failure of the endometrium to respond to normal hormone stimulation; ovarian failure; and pituitary failure.

A careful history and physical examination are most essential. The size of the clitoris and uterus and ovaries is noted. The uterocervical ratio is determined. Also the basal metabolic rate, and blood cholesterol determinations, x-ray examination of the skull, and when indicated, an introvenous pyelogram. Finally, the patient is instructed to take daily rectal temperature before arising.

To date, every patient has been made to bleed eventually. Twenty per cent of the patients menstruated after thyroid therapy alone or combined with weight reduction. Of 39 patients who failed with this mode of therapy, 25 responded to a course of progesterone Linguets, that is, 50 mg. daily for four days. Of 14 patients who did not respond to this type of therapy, all eventually menstruated after the completion of the twenty-one-day course of estrogen and the four-day course of progesterone Linguets. No direct cause for the amenorrhea, other than hypothyroidism, was discovered in any case. The large number of patients who gave a history of a normal pregnancy suggests pituitary or ovarian suppression or exhaustion.

There is some indication that cyclic administration of progesterone has a stimulative effect on ovulation in the subsequent cycle if it is considered that almost 50 per cent of patients who responded to progesterone, but not to thyroid, ovulated. Further follow-up study will be of value in permitting definite conclusions in this regard. JAMES P. MARR.

Gyarmati, E.: Amenorrhea in Concentration Camp, Minerva Ginec. 4: 381, September, 1950.

After a survey from the literature on the so-called "amenorrhea of war" the author describes his personal studies carried on in a Russian concentration camp from 1946 to 1950. Among 1,300 women he found 606 suffering from amenorrhea (46 per cent). For the etiology the first place is given to psychic trauma and to individual predisposition; alimentation and stress are only contributory factors. Frequency, duration, and symptomatology are then discussed with details, in respect to the age of women.

The author believes that the emotional factors cause neurovegetative disorders, taking origin in the diencephalon and acting on the hypophysis in such a way as to cause the arrest of the ovarian activity and consequently amenorrhea. RINA D'AMICO.

Moon, A. A.: Dysmenorrhea and the Climacteric; Psychosomatic Assessment and Treatment, M. J. Australia, p. 174, Feb. 11, 1950.

Many of the phenomena of primary dysmenorrhea and the climacteric can be explained on a somatic basis. Perhaps increased knowledge of anatomy and biochemistry will result in less emphasis on psychogenic factors. Each patient is assessed individually. The author feels that recourse to expert psychiatric examination is usually unnecessary, but it is suggested that consultation with the psychiatrist should be obtained before a patient is submitted to a major surgical operation such as sympathectomy. It is felt that overemphasis on psychogenic causes are not in the best interests of the patient. The author stresses the need for organized medical education of girls at puberty. He also stresses the need for educating women before the onset of the menopause. WILLIAM BERMAN.

Newborn

Bryce, Lucy M., Campbell, Kate, Graydon, J. J., Jakabowicz, Rachel, and Kiel, Lorna: The Effect of Heterospecific Pregnancy on the Hemoglobin and Red Cell Levels in the New Born Infant, M. J. Australia, p. 337, Sept. 3, 1949.

The authors show that among babies whose ABO or Rh factors or both are incompatible with these factors in their mothers the hemoglobin levels are lower on the first and the third days and in the sixth week than those in which there is no incompatibility. In cases of ABO compatibility with Rh incompatibility there is a reduction in the mean hemoglobin level both on the first and the third days and again in the sixth week. Similarly ABO incompatibility without Rh incompatibility causes a lowering of the mean hemoglobin level at each of these times. A double incompatibility, however, appears from this analysis to cause a lowering of the mean hemoglobin level not greatly in excess of that caused by a single incompatibility. It is usually assumed that the action of incompatible maternal blood factor antibodies on the fetal cells is hemolytic. It is postulated that the iron liberated from the fetal cells becomes distributed through both fetal and the relatively much larger maternal circulation and that in the latter it may be partly, at any rate, utilized for maternal erythropoiesis. Other possibilities are that the maternal antibodies may have a deleterious effect not only on the red cells with resultant hemolysis, but also on the other cells, one result of which is to render the fetal hematopoietic tissues unable to resynthesize the liberated iron, or that, as a result of persistent destructive action by the antibodies, fetal red cells as they are developing are broken down before hemoglobin formation is complete. WILLIAM BERMAN.

Physiology of Pregnancy

Lucia, S. P., and Hunt, Marjorie L.: Hematologic Features Which May Influence Rh Immunization, California Med. 73: 250, 1950.

The biologic features which may influence Rh sensitization in the mother and hemolytic disease in the newborn are conditioned by the hereditary immunologic pattern of the subjects, the antigenic characteristic of the blood group specific substances, the character of the antibody responses, the inherent susceptibility to disease as a result of the immune mechanism, and the character and sequence of exposure to the antigenic substance. In respect to Rh-negative women, there appears to be a greater vulnerability to immunization among those of blood group A. In regard to the infant, the compatibility of the maternal-infant blood types and the part they play in the phenomenon of the competition of antigens may influence the occurrence of hemolytic disease in the newborn.

JAMES P. MARR.

Pregnancy, Complications

Solomons, Edward: Treatment of Varicose Veins in Pregnancy. A Critical Survey of Injection Treatment Based on 600 Cases Treated at the Rotunda Hospital, Irish J. M. Sc. No. 296, Sixth Series, August, 1950.

The author discusses the treatment of 598 patients with varicose veins. Four hundred fifty of these were treated by injection and 148 by paste and other noninjection methods. Complications were nonexistent in the hands of these physicians. Temporary benefit was striking and almost universal with the injection treatment. This was true also of injection of the vulvar veins, 74 patients being treated for this condition. Of 182 patients treated with injection during pregnancy, 53 per cent showed permanent cure.

LOUIS M. HELLMAN.

Martland, H. S., and Martland, H. S., Jr.: Placental Barrier in Carbon Monoxide, Barbiturate, and Radium Poisoning, Am. J. Surg. 80: 270, 1950.

This very provocative report from a medical examiner's laboratory includes observations on human poisons of great interest for their bearing on obstetrical problems.

A. Two cases of suicide by gas poisoning by pregnant women are reported in which examination of fetal blood failed to reveal evidence of carboxyhemoglobin. The authors conclude that the gas is so bound by the hemoglobin in the red cells that it is not available for diffusion through the placenta; they also offer this evidence to refute those who postulate placental transfer of red cells to explain Rh phenomena.

B. A case of barbiturate poisoning with higher levels of drug in fetal than maternal tissues is used to underscore the belief of the essayists that the use of barbiturates in labor is extremely dangerous and regrettable.

C. A review of some of the senior author's work with radium poisoning in human beings is then presented with a survey of some of the children of these former radium-dial workers. Tests for radioactivity in these children failed to show any significant transfer.

S. B. GUSBERG.

Pregnancy, Toxemia

Assali, N. S., and Prystowsky, Harry: The Effect of Adrenergic Blockade With a Benzodioxane Derivative, 933F, on Hypertension of Toxemia of Pregnancy, Surg., Gynec. & Obst. 90: 655, 1950.

The work of Assali and his colleagues has shown, previously, that autonomic blockade with either tetraethylammonium chloride or high selective spinal anesthesia results in a negligible fall in blood pressure in toxemia of pregnancy. This led these investigators to

the conclusion that in this disease blood pressure elevation is maintained principally by humoral mechanisms. The use of piperidylmethyl benzodioxane as a possible adrenalytic was tried in 5 patients with acute toxemia. Five normal patients served as controls. There was no fall in blood pressure in either the normal or toxemic pregnant patients with this drug. The authors, therefore, conclude that Adrenalin plays no role in the maintenance of normal blood pressure in either normal or toxemic patients, and is not the sought-for humoral agent. LOUIS M. HELLMAN.

de Watteville, H.: Toxemia of Pregnancy in Relation to Coagulation of the Blood, Gynec. et obst. Supplement, Bull. Assoc. d. gynéc et obst. de langue franç., p. 154, April, 1950.

Eclampsia is characterized by convulsive crises in which definite lesions of many organs are noted. On autopsy, in these structures, involvement of the blood vessels is one of the most constant findings. The author believes that these changes result from changes in the coagulation properties of the blood. As evidence of this, a marked increase in the prothrombin level was found in a large percentage of cases of toxemia of pregnancy as compared with the findings in normal gravidity.

On the basis of these facts, the author has administered in severe cases of toxemia of pregnancy a total of 450 mg. of heparin over a period of three consecutive days and has found results obtained to be very encouraging. His work has been partially corroborated by others who found experimentally that the injection of thrombokinase in animals produced lesions similar to those found in human eclampsia and that these experimental lesions could be obviated by simultaneous therapy with heparin. L. B. WINKELSTEIN.

Panella, Italo: Thromboplastic Activity of the Chorion and Dicumarol, Minerva Ginec. 4: 364, September, 1950.

Recently, heparin and Dicumarol have been used in treatment of toxemia of pregnancy, following the suggestion of Schneider (1947), who attributes the cause of such a disease to toxic action of a placental substance similar to thromboplastin.

In fact, the placenta is very rich in a substance possessing thromboplastic activity and its extracts injected in animals give a picture very similar to that of toxemia in pregnant women and may be prevented by simultaneous administration of heparin.

The author studied the action of Dicumarol in pregnant rabbits and obtained a remarkable decrease of the chorionic thromboplastic activity. But he states that Dicumarol is not advisable in toxemia of pregnancy, because of its high toxicity on the mother and fetus and heparin only may be tried in suitable cases. RINA D'AMICO.

Anselmino, K. J., and Stewens, R.: Treatment of Hypertension and Kidney Disease During Pregnancy by Means of Peridural Infiltration, Neue Medizinische Welt, N/R 27/28, 950, July 15, 1950.

Twenty-three cases of hypertension, kidney involvement, and eclampsia in pregnant women were studied and treated by means of peridural infiltration. The method employed consisted of the bilateral injection, peridurally, of from 2 to 3 c.c. of local anesthetics covering the 4 spinal cord segments in the kidney region. It was found that in order to avoid unfavorable reactions, the injection must be given slowly.

The effects of the injections are manifested by a marked vasodilatation and a drop in blood pressure. These effects are noted in from 10 to 15 minutes after injection has been given and last for 6 to 10 hours. The drop in blood pressure is marked and averages from 50 to 60 mm. Hg systolic, and from 30 to 40 mm. Hg diastolic only in those cases where hypertension is present. Where the blood pressure is normal peridural infiltration does not result in any change or at most in an evanescent drop which returns to normal in 20 to 30 minutes.

The physiological mechanism of this procedure is not clearly understood. However, it is believed that the favorable reactions obtained are the result of a peripheral vasodilatation together with a dilatation of the blood vessels of the kidney. In most cases this was manifested by a marked diuresis.

No deleterious effects were encountered except an occasional mild anaphylactic reaction. In all of the cases studied, all symptoms and findings responded favorably and further procedures for maintenance of the pregnancy or delivery were carried out with ease and safety.

This work is confirmatory of previous similar studies by American investigators using spinal anesthesia. L. B. WINKELSTEIN.

Sterility, etc.

Meaker, S. R.: Ovarian Resection for the Relief of Sterility, Fertility and Sterility 1: 293, 1950.

The author presents a series of 65 patients with polycystic ovaries treated with wedge resection in a 20-year period. He briefly reviews the endocrine and mechanical factors that have been suggested to be of etiological importance and expresses his preference for the former theory.

In discussing the primary symptoms of amenorrhea and sterility the essayist noted no significant correlation with pelvic pain in this group of patients with enlarged cystic ovaries.

The operative treatment by ovarian resection was found to be effectual in initiating normal menstruation and relieving infertility in the majority of cases. S. B. GUSBERG.

Vaginal Infections

Vayssieren, E., and Salignon, Andre: Vulval Vaginal Mycoses, Bull. Assoc. d. gynéc. et obst. de langue franç., p. 197, Feb. 28, 1950.

A study was made of 442 cases of vaginal mycotic infections, 338 of which occurred in pregnant women. The authors feel that the pH of the vaginal secretion does not play a role in the development of the infection, since normal vaginal acidity runs between 4.5 and 6.1 and with both Monilia and Trichomonas the pH is approximately 5.8. Since these infections are more common in the pregnant woman, a question of hormonal causation arises. In vitro, none of the hormones studied had any effect on the growth or inhibition of growth of the mycotic organisms. However, changes in the vaginal mucous membrane and in the glycogen content of the vaginal cells result from interreaction of follicular and luteal hormones, which changes may be demonstrated both during pregnancy and in the second half of the menstrual cycle.

With this rationale as a basis for therapy, attempts at controlling or curing the infection were made with injection of testosterone both in pregnant and nonpregnant women. Contradictory results were obtained and the authors believe that the best methods of treatment still utilize frequent application of various antiseptics and dyes to the vagina.
L. B. WINKELSTEIN.

Necrology

JAMES RAMSDELL BLOSS, M.D., a member of the Advisory Editorial Board of the JOURNAL for many years, died at his home in Huntington, West Virginia, on April 23, 1951, after a prolonged illness, at the age of 71. Known for his efforts in improving obstetric care in his community, he served as Secretary, and later, President of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, was Secretary and later Chairman of the Section on Obstetrics and Gynecology of the American Medical Association, as well as a Trustee and Vice-President of the latter.

Born in 1881, in Ceredo, West Virginia, he received his M.D. degree at the University of Virginia, in 1905, and was long associated with the Huntington Memorial Hospital as attending obstetrician and President of its Staff in 1934. He was also Editor of the West Virginia Medical Journal, 1927-1951.